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ARTERIOSCLEROSIS AND PARTIAL OBSTRUCTION OF THE MAIN RENAL ARTERIES IN ASSOCIATION WITH "ESSENTIAL" HYPERTENSION IN MAN[1]

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Submitted for publication June 27, 1939

The experimental work of Goldblatt and his associates (1–6), and the experiments of others[2] have proved that partial occlusion of the main renal arteries causes persistent hypertension of marked degree in a variety of animals, including the rat, rabbit, dog and monkey. It seems possible, therefore, that in man arteriosclerotic plaques in the main renal arteries may obstruct the vessels and play a part in the pathogenesis of some examples of hypertension. A few cases of this character have been described recently. Moritz and Oldt mention a case in which the mouths of the main renal arteries in the aorta were narrowed by arteriosclerotic plaques (18). Leiter described a case in which one renal artery was occluded and the other was narrowed by arteriosclerotic lesions (19). Freeman and Hartley observed the development of hypertension in a patient after the operative removal of one kidney, and at autopsy found the opposite renal artery to be sclerotic and partly occluded (20).

A number of cases have recently been autopsied at The Johns Hopkins Hospital and have been demonstrated by Dr. A. R. Rich at Clinical-Pathological Conference, in which there was a clinical history of "essential" hypertension, and at autopsy the renal arteries were found to be constricted near their attachment to the aorta. The main renal arteries were, therefore, examined in all of the cases of "essential" hypertension among the specimens used for teaching pathology at the

[1] A preliminary report of this study was made at the post-graduate meeting of the American College of Physicians in Baltimore on March 14, 1939, and at the Sixty-Fourth Meeting of the Interurban Clinical Club in Baltimore on April 15th, 1939.

[2] For complete references to the literature see Goldblatt, Kahn and Hanzal (7).

Medical School. In a surprising number the arteries were found to be sclerotic and partly occluded.

Terminology: The term "essential" hypertension, as used in this paper, is meant to indicate a form of chronic hypertension which, as described by Fishberg, is of unknown cause, and is followed in some of the cases by diminishing renal function and certain characteristic structural changes in the kidneys (8). The form of Bright's disease which develops is familiar as arteriosclerotic and arteriolosclerotic nephritis (9), and will occasionally be spoken of in this paper as "vascular" nephritis.

MATERIAL EXAMINED

The series of cases examined comprises fifty examples of essential hypertension and fifty control cases without hypertension. The age distribution of the cases according to decades, and the race and sex are given in Table 1.

The patients in the group with hypertension varied in age from 28 to 89 years. In twenty-two of the cases of hypertension clinical and microscopical evidence of nephritis was lacking; and none of the generally recognized causes of hypertension was found at autopsy. In twenty-eight cases the renal function was impaired and the microscopical lesions of arteriosclerotic and arteriolosclerotic nephritis were found in the kidneys. Twenty-four of these patients died in uremia.

In two cases (16069 and 14857, Table 3), despite known chronic hypertension, relatively little cardiac hypertrophy was found at autopsy. In the other cases of hypertension in the series the left ventricle of the heart was considerably or greatly hypertrophied, in the absence of any valvular stenosis or insufficiency, congenital abnormality, or other recognized cause of cardiac hypertrophy. Tables 2, 3 and 4 include the known duration of hypertension, the usual range of variations in the blood pressure as recorded in the clinical histories, and the weight of the heart in each case.

The entire length of each renal artery was not available for examination in most of the cases. It has been customary at autopsy to remove the kidneys, ureters and pelvic organs together. The aorta is usually removed separately, and during this procedure a consider-

able portion of each renal artery may be cut off. The stumps of the arteries left attached to the aorta for examination in this series varied in length from a few millimeters to about 3 centimeters. In a few cases most of one renal artery was found attached to the kidney, but usually only short branches of the artery were left at the hilum.

The arteries were examined by making a number of parallel cross sections with a sharp knife. Blocks for microscopical sections were cut through the point of greatest narrowing. The material had

TABLE 1

The Distribution of Sex, Race, and Age among Fifty Cases of "Essential" Hypertension and Fifty Control Cases

	NUMBER OF CASES	
	Hypertension (50 cases)	Controls (50 cases)
Sex:		
Males	28	28
Females	22	22
Race:		
Colored	22	13
White	28	37
Age:		
3rd decade	2	2
4th decade	10	11
5th decade	12	12
6th decade	10	12
7th decade	9	11
8th decade	5	2
9th decade	2	0

usually been fixed in Kaiserling's fluid for widely varying periods before the blocks were cut. The latter were dehydrated in the usual manner, and sections were stained with haematoxylin and eosin.

It should be emphasized that only by cutting cross sections of the arteries was it possible to appreciate the degree of stenosis caused by arteriosclerotic plaques. When, as in some cases, the vessels were found opened longitudinally even large plaques seemed relatively insignificant and the arterial lumen widely patent. Cross sections

TABLE 2

Marked or Extreme Stenosis of One or of Each Main Renal Artery

AUTOPSY NO.	RACE	SEX	AGE	KNOWN PERIOD OF HYPERTENSION	USUAL RANGE OF BLOOD PRESSURE	VASCULAR NEPHRITIS	HEART WEIGHT	RIGHT RENAL ARTERY		LEFT RENAL ARTERY	
								Outside diameter	Size of lumen	Outside diameter	Size of lumen
					mm. Hg		gm.	mm.	mm.	mm.	mm.
10508	C	F	43	1 wk.	220/130–255/155	+	750	7 x 5	3 x 3.5	7 x 5	4 x 0.5 to 2
11553	C	M	28	1 wk.	180/120–220/130	+	450	5	3 x 1.5	5	4 x 1
11922	C	M	49	3 mo.	190/ 90–250/130	0	460	10 x 7	7 x 1.5 to 2	5	Occluded
14546	C	F	49	2 yr.	180/130–260/140	+	555	8 x 6	Occluded	5	3 x 1.5
14554	W	M	29	2 wk.	196/138–240/160	+	600	5	3	7 x 4.5	3 x 1.5
15486	W	M	50	2 yr.	254/130–300+	+	550	7 x 6	4 x 3	8 x 6.5	4 x 2.5
15509	C	F	39	7 yr.	165/110–280/140	+	570	7 x 4.5	1.5	6.5 x 5.5	2.5 x 1.5
15523	C	F	31	2½ yr.	165/130–310/110	0	830	7 x 4.5	4 x 2	9 x 8	4.5 x 4
15537	W	F	41	5 yr.	220/150–268/160	+	550	6 x 5.5	4.5 x 2.5	9 x 7	6 x 2
15577	W	M	70	4 mo.	165/105–210/130	0	740	6	5 x 1	9 x 7	4
15588	W	M	60	3 wk.	204/140–230/150	+	450	6.5 x 5	4.5 x 3	7 x 6	5 x 1.5
15612	W	F	68	6 mo.	150/100–180/110	0	480	7 x 5	3 x 1.5	6 x 4.5	2 x 1.25
15652	C	M	80	8 mo.	168/ 90–190/100	0	475	9 x 6	3.5 x 3	7 x 6	2.5
15823	W	M	30	5 wk.	210/120–240/150	+	650	8 x 6	4	7 x 6	3 x 1.5
15872	W	M	52	15 yr.	160/110–200/140	0	660	6.5 x 6	4 x 1.5	Cut off	
15881	W	F	50	10 yr.	152/ 82–196/110	+	400	5 x 3	2 x 0.5	7 x 6	3 x 2
15928	W	M	67	1 mo.	200/125–270/130	+	560	9 x 6.5	5 x 2.5	9 x 6.5	5 x 2.5
15935	W	M	50?	1 wk.	270/160–300/160	+	700	8 x 6.5	3.5	7 x 5	3 x 1
15937	W	M	50	15 mo.	230 –260/190	+	800	2 arteries each 3.5 x 3	Each 2.5 x 2	4.5 x 4	Less than 1
15997	W	M	63	4½ yr.	172/ 90–200/110	0	610	9 x 5	7 x 2.5	9 x 7	6 x 2.5
16079	C	F	40	4 mo.	205/120–220/120	0	420	7.5 x 5	4 x 1	Cut off	
16097	W	M	34	1 wk.	190/110–230/200	+	820	7	5 x 2	7 x 6.5	3 x 2
16153	W	F	72	8 yr.	164/ 80–180/ 90	0	380	6	3 x 2	7 x 6	5 x 3
16166	W	M	33	2 mo.	155/118–240/175	0	400	6 x 4.5	2 x 1.5	Cut off	
16184	W	M	56	1 wk.	170/115–170/130	0	500	6	3.5 x 2	7	4
16237	C	M	53	3 yr.	150/105–200/140	+	580	5 x 3.5	2.5 x 1.5	5	2 x 1.5
16386	C	F	64	2 yr.	160/ 70–240/140	0	400	7 x 4.5	5 x 2.5	6.5 x 4.5	3.5 x 0.5 to 2

TABLE 3

Moderate Stenosis of One or of Each Main Renal Artery

AUTOPSY NO.	RACE	SEX	AGE	KNOWN PERIOD OF HYPERTENSION	USUAL RANGE OF BLOOD PRESSURE	VASCULAR NEPHRITIS	HEART WEIGHT	RIGHT RENAL ARTERY		LEFT RENAL ARTERY	
								Outside diameter	Size of lumen	Outside diameter	Size of lumen
					mm. Hg		*gm.*	*mm.*	*mm.*	*mm.*	*mm.*
10240	C	F	44	3 yr.	150/100–268/182	+	650	8 x 5	5 x 2.5	11 x 6	8 x 3
14857	W	F	79	1½ yr.	140/114–220/140	0	350	6	3	6	4
15180	C	F	36	2 yr.	156/ 94–300/200	+	770	6	4 x 3	7.5 x 6	5 x 3.5
15704	W	M	47	4 yr.	162/110–234/140	0	450	6	4	8 x 5.5	6 x 2.5
16016	W	F	67	5 mo.	172/ 80–190/ 90	0	525	8 x 6	6 x 3	9 x 6	6 x 3.5
16028	W	F	47	4 da.	198/146–268/170	+	375	Cut off		6	3
16069	W	M	75	14 yr.	170/100–240/140	0	340	10.5 x 5.5	8 x 3	8 x 7	6 x 4
16070	W	M	77	4 mo.	170/ 80–200/ 90	0	550	7.5 x 6	6 x 3	Cut off	
16150	W	M	89	3 wk.	148/105–170/100	0	460	7 x 5	4 x 3	7 x 6	4.5 x 3.5
16151	W	M	51	8 mo.	160/100–220/120	0	460	Cut off		7.5 x 5	4 x 3
16179	C	F	56	4½ yr.	200/110–294/160	+	680	6.5	3.5	6.5	3.5
16207	C	F	32	9 yr.	150/105–230/164	+	550	7 x 5	3.5 x 3	Cut off	
16230	C	F	65	2 wk.	240/110	0	450	7.5 x 5	5 x 2	6 x 4.5	4.5 x 3.5
16231	W	M	65	3½ yr.	152/ 90–188/116	0	660	6 x 5.5	3.5 x 3	6 x 5.5	3.5 x 2.5
16271	C	F	30	10 da.	220/135–275/160	+	540	6.5 x 4	5.5 x 3	6	3
16257	W	F	36	1 mo.	160/140–260/184	+	380	5 x 4	3.5 x 3	6 x 4	3 x 2

TABLE 4

Slight Narrowing of the Main Renal Arteries

AUTOPSY NO.	RACE	SEX	AGE	KNOWN PERIOD OF HYPERTENSION	USUAL RANGE OF BLOOD PRESSURE	VASCULAR NEPHRITIS	HEART WEIGHT	RIGHT RENAL ARTERY		LEFT RENAL ARTERY	
								Outside diameter	Size of lumen	Outside diameter	Size of lumen
					mm. Hg		*gm.*	*mm.*	*mm.*	*mm.*	*mm.*
15268	C	M	42	1½ yr.	180/130–240/140	+	750	12 x 5	9.5 x 3	9 x 5	7 x 3
15453	W	M	46	4 yr.	166/104–240/140	+	650	8 x 5	5.5 x 4	8 x 5	5.5 x 4
15958	C	M	68	10 mo.	170–210/95	0	400	6 x 3.5	4.5 x 2	5.5	4
16162	C	F	31	1 mo.	170/130–300+/180	+	350	6 x 4	5 x 2.5	7.5 x 5	5 x 3
16245	C	M	55	1½ yr.	160/110–278/180	+	570	9 x 5	7 x 3	7 x 6	5 x 4
16275	C	F	42	4½ yr.	178/118–268/180	+	660	7.5 x 6	5 x 4	7.5 x 6	5 x 4
11441	C	M	42	1 da.	220/120–230/132	+	860	5.5	3	Cut off	

made through the same plaques, however, showed the arteries to be actually very narrow or nearly occluded in localized areas.

RESULTS

A. Cases of Hypertension

In the majority of the cases of hypertension in this series there was partial occlusion of the lumen of one or of both the main renal arteries. The stenosis of the lumina was usually caused by ordinary yellowish-white arteriosclerotic plaques. In some vessels the plaques were calcified. The lesions were usually excentric in position and they were particularly thick along a portion of the circumference of the artery. The narrowed lumina were therefore generally irregular in shape and position.

The plaques of sclerosis in most cases were largest and most numerous in a short segment of each artery near the aorta. Beyond this localized region the portion of the vessel that remained usually contained no large atheromatous plaques. In one case, however, there were sclerotic changes throughout both main renal arteries, and large yellow plaques were found even in the arterial branches at the hilum of each kidney. In two cases, besides arteriosclerotic changes, there were old thrombi which almost completely occluded the already narrowed arteries. In a good many cases the orifices of the arteries were further narrowed by arteriosclerotic plaques in the aorta.

The arteriosclerotic lesions in the main renal arteries were part of a general arteriosclerosis in every case. The aorta was sclerotic in each case, and in most of the cases other arteries, such as the coeliac axis, the superior mesenteric, iliac and coronary arteries showed varying degrees of arteriosclerosis. The localization of sclerosis and stenosis to short segments of the main renal arteries near the aorta, more or less continuous with similar lesions in the aorta itself, was conspicuous in all of the cases in which the vessels were narrowed.

The cases of hypertension have been divided into three groups (Tables 2, 3 and 4) according to the degree of stenosis of the main renal arteries, whether marked, moderate, or slight. The tables show the outside diameter of each artery and the size of the remaining lumen. These measurements were made from stained microscopical preparations of cross sections of the vessels. They are not abso-

lutely accurate, since they were made by means of a millimeter rule and a hand lens. In a few of the cases the arteries were opened longitudinally at autopsy and consequently the cut edges could not be exactly approximated in cross section. The photographs may perhaps show more clearly than these measurements the degree of obstruction caused by the arteriosclerotic plaques.

In the first group, the cases in which very marked stenosis of the main renal arteries was found, there are twenty-seven cases or 54 per cent of the number examined (Table 2). The lumina of both renal arteries in five of these cases were reduced to narrow clefts measuring 1.5 millimeters or less in width. In eleven cases the lumen of one renal artery was extremely stenosed, measuring 1.5 millimeters or less in width, while the opposite artery was either markedly or moderately or slightly narrowed, or was cut off and could not be examined (2 cases). The remaining eleven cases in this group showed marked stenosis of one or of each main renal artery. The lumina, however, were more than 1.5 millimeters in diameter.

In all but one of the cases in this group the difference between the inside and outside diameter of each very narrow main renal artery varied from 4 to 6 millimeters. This may afford some idea of the size of the arteriosclerotic plaques which projected into the vessels. In the exceptional case (16237, Table 2; and Figures 1 and 2, Plate II) the main renal arteries were small, measuring only 5 x 3.5 and 5 x 5 millimeters in outside diameter respectively. The difference between inside and outside diameter of these arteries varied from 2.5 to 3.5 millimeters, and the lumen of each was very much narrowed (1.5 millimeters in width).

The second group contains sixteen cases or 32 per cent of those examined (Table 3). In four of these cases one artery was cut off and could not be examined, while the opposite artery was moderately narrowed. In nine cases the segment of one artery that remained attached to the aorta was either slightly narrowed or normal and the other artery was moderately narrowed. The three remaining cases in this group showed a moderate degree of stenosis of both main renal arteries. The difference between inside and outside diameter of the moderately narrowed arteries varied from 3 to 3.5 millimeters.

In most of the cases in the third group of seven (14 per cent) the

stumps of the renal arteries available for examination showed some sclerosis and intimal thickening without much reduction in the lumina. In this group the difference between the inside and outside diameter of the arteries varied from 1 to 2.5 millimeters. The vessels exhibiting a difference of only 1 millimeter between inside and outside diameter were essentially normal.

To summarize these figures, in forty-three of the cases of hypertension (86 per cent) arteriosclerotic plaques were found either in one or in each of the main renal arteries. The lesions caused localized partial occlusion which varied in degree from a moderate to an extreme stenosis of the vessels. In the remaining seven cases, 14 per cent of the number studied, the segments of the arteries that could be examined were not apparently narrowed to a significant degree.

The Main Renal Arteries in Cases of Essential Hypertension with and in those without Vascular Nephritis. In the present series of fifty cases the clinical signs of impaired renal function and the microscopical lesions of vascular nephritis were present in twenty-eight cases (56 per cent). In ten of these cases hypertension was known to have existed for a long time before renal impairment developed. In the remainder (eighteen cases) renal function was impaired when the patients were first examined.

No striking difference was found in the incidence and degree of stenosis of the main renal arteries in the cases of hypertension with vascular nephritis and in those without nephritis. Among the twenty-eight cases of vascular nephritis there were sixteen (57 per cent) with marked stenosis, seven (25 per cent) with moderate and five (17 per cent) with slight narrowing of the lumen of one or of each of the main renal arteries.

Of the twenty-two cases of hypertension without vascular nephritis, twelve (54 per cent) showed marked, nine (40 per cent) moderate, and one (4 per cent) slight narrowing of one or of each of the renal arteries.

Arteriosclerosis of the Intrarenal Branches of the Renal Arteries. In all of the cases of hypertension in this series old arteriosclerotic changes were found in the larger branches of the renal arteries in the kidneys, i.e., the interlobar, arcuate and interlobular arteries. The arteriosclerotic process consists of the familiar thickening of the intima and reduplication of the internal elastic layer in association with

deposits of lipoid substances here and there; and as a result more or less hyaline layers of tissue are formed which encroach on the lumina of the affected arteries. These changes in the intrarenal arteries of subjects with hypertension are well known. They have been described and discussed recently by Williams and Harrison who found them to be more marked in the kidneys of hypertensive individuals than in the controls (10).

The degree of arteriosclerosis of intrarenal arteries was variable in the different cases of the present series, and also in the various intrarenal branches of individual cases. No attempts were made to estimate the amount of intrarenal arteriosclerosis in each case or to correlate sclerosis of the intrarenal arteries with narrowing of the main renal arteries. It may be said, however, that in some of the cases it was readily evident that sclerosis of intrarenal arteries was not paralleled by that of the main arteries. In other cases, with marked sclerosis and narrowing of the main arteries, changes in the intrarenal branches were comparatively slight.

Some degree of hyaline sclerosis of the terminal renal arterioles was also found in all of the cases of hypertension and in every case hyaline arterioles were found in other tissues, such as the pancreas and about the adrenals. A marked degree of generalized arteriolosclerosis was not found in every case, however, and in some instances there were relatively few hyaline arterioles either in the kidneys or other organs.

The Relation between Stenosis of Main Renal Arteries and the Occurrence of Acute Necrosis of Renal Arterioles. The experiments of Goldblatt (5), Wilson and Pickering (11) and of Wilson and Byrom (12) have shown that, under the conditions of the experiments, hypertension is one of the factors in the pathogenesis of acute arteriolar necrosis, since the lesions develop in arterioles of various tissues after the appearance of experimental hypertension and since they are not found in the kidneys whose renal arteries are partially occluded. It would therefore be interesting to determine whether or not there is any relation between the degree of stenosis of the main renal arteries and the occurrence of acute arteriolar necrosis in the kidneys of the human being.

In man, in the presence of essential hypertension, these lesions in the renal arterioles are usually found only in cases with impaired renal

function and vascular nephritis. The present series contains twenty-eight cases (56 main renal arteries) in which there was evidence of vascular nephritis and in which therefore necrotic renal arterioles might be found. One renal artery of each of three of these cases was cut off at autopsy and could not be included in this study.

In the remaining group of fifty-three renal arteries fourteen were extremely narrowed. The lumen of each very narrow artery measured 1.5 millimeters or less in width. The lesions of acute arteriolar necrosis were found in only four of the fourteen corresponding kidneys, an incidence of 28.5 per cent. The lumina of the other thirty-nine main renal arteries of the group were all narrowed but were more than 1.5 millimeters in least diameter, and necrotic arterioles were found in thirty-four of the corresponding kidneys (87 per cent).

B. Controls

The controls consist of fifty cases in which no history of hypertension was obtained, the blood pressure as recorded in the clinical histories was not elevated, and there was no evidence of cardiac hypertrophy at autopsy. The patients in the control group varied in age from 28 to 78 years. The age distribution of the patients in decades does not differ materially from that of the fifty cases of hypertension (Table 1). Death was caused in these cases by a variety of diseases.

The renal arteries of the control cases were examined, fixed, stained and measured like the arteries of the cases with hypertension. In forty-five of the control cases the size of the lumen of each artery was practically normal. The difference between the inside and outside diameter of the vessels varied from 1 to 2 millimeters.

In five of the control cases (10 per cent) arteriosclerosis and partial obstruction of the main renal arteries was found. Both arteries were very sclerotic and stenosed in one case (14511), a man of 63 years who died with carcinoma of the bladder, pyonephrosis and chronic pyelonephritis. The blood pressure was 130/80. The heart was atrophied and weighed only 225 grams. In both kidneys many of the intrarenal arteries showed thickened intima and narrowed lumen. No evidence of generalized arteriolosclerosis was found.

In a second case (16158), a man 45 years old who died from carcinoma of the bladder, the blood pressure was 124/78. One main

renal artery was moderately narrowed by arteriosclerosis; the other was slightly changed. The intrarenal arteries were normal and there was no generalized arteriolosclerosis. The heart was atrophic, and weighed 220 grams.

A moderate amount of arteriosclerosis and narrowing of one main renal artery was found in a third case (16165). The other artery was unusually wide (7 x 5 mm., inside diameter). The patient was a man 67 years old who died with generalized peritonitis which followed rupture of a recto-vesical fistula. The blood pressure was not elevated during the patient's stay of one day in the hospital, and had been normal three years before. The heart was not hypertrophied. The intrarenal arteries showed a little sclerosis, and a few hyaline arterioles were found in the pancreas and capsule of the adrenal.

In each of two examples of polycystic kidneys (15438 and 16085) one main renal artery was markedly stenosed by arteriosclerotic plaques, and the other was slightly narrowed. Both patients died in uremia, but the blood pressure was not elevated and at autopsy the heart was not hypertrophied in either case. In one of these cases there was very little sclerosis of intrarenal arteries, and no evidence of general arteriolosclerosis was found. In the other case the pancreas contained a good many hyaline, narrowed arterioles and there were a few about the adrenal. Little evidence of sclerosis of intrarenal arteries was found.

C. Cases of Uncertain Classification

It is necessary here to describe briefly four cases which cannot be grouped either with the examples of chronic hypertension or with the controls whose blood pressure was normal.

Case 1 (15527), a colored man 64 years old. In 1932 the blood pressure was found to be elevated, 180/110. In 1933 the pressure was 152/80. In 1937 the patient died with congestive heart failure which followed long-standing emphysema The blood pressure during the final illness was not above 106/76.

At autopsy the heart weighed 350 grams. The right side was greatly hypertrophied, but the wall of the left ventricle was not hypertrophied at all. There was marked arteriosclerosis of the aorta. The main renal arteries were sclerotic and both were moderately stenosed near the aorta. The arteries of medium size and the terminal arterioles in the kidneys, pancreas, and about the adrenals showed a fairly marked degree of sclerosis and narrowing.

Case 2 (15901), a white woman 54 years old. The family physician stated that 25 years ago her systolic blood pressure had been in the neighborhood of 200 mm. Hg. From then on he had examined her on the average of once or twice a year and had always found the blood pressure elevated.

During the last year and a half of her life the patient was admitted to The Johns Hopkins Hospital three times. On each admission the signs and symptoms of congestive heart failure were present and the blood pressure was elevated, usually around 160–170 mm. Hg systolic and 110–120 mm. Hg diastolic. As the oedema disappeared and the patient improved, the blood pressure always returned to normal.

At autopsy the heart weighed 630 grams. The coronary arteries were sclerotic and occluded in places. There were old infarcts and other scars in the myocardium. The aorta was sclerotic throughout and both main renal arteries were moderately narrowed by arteriosclerotic plaques. The interlobular arteries in the kidneys showed slight sclerosis and there were a few hyaline arterioles in the pancreas and about the adrenal.

Case 3 (15616), a white woman 57 years old who was admitted to the hospital with weakness, chronic cough, jaundice, and diabetes. She died following a large hemoptysis. The blood pressure, taken twice in eleven days, varied from 106/62 to 155/90.

The autopsy showed a chronic bronchial infection which extended through the lung and into the aorta. The heart was small (270 grams). The aorta was very sclerotic. The lumen of the left renal artery was moderately stenosed. The right was nearly occluded by a large plaque. The lumen that remained was a narrow cleft measuring 4 x 1 mm. Microscopically there was moderate sclerosis of the large and medium sized arteries in the kidneys, and fairly marked hyaline sclerosis of arterioles in the adrenal capsule.

Case 4 (16301), a white man 67 years old with signs of senile dementia, nocturia, frequency of urination, and difficulty in emptying the bladder. The blood pressure varied from 128/80 to 144/100. He died following the onset of signs of infection in the lung.

The autopsy showed a large area of gangrene and cavity formation in the right lung. The prostate was moderately enlarged but the bladder and ureters were not dilated. The heart weighed only 240 grams. The coronary arteries were very sclerotic. The anterior wall of the left ventricle and the apical part of the interventricular septum were scarred and thin, forming an aneurysmal area at the apex of the heart. The aorta was extremely sclerotic. The main renal arteries were sclerotic and there was marked stenosis of the lumen of each one.

In summary these four cases showed at times varying degrees of hypertension. There was sclerosis and stenosis of one or both of the main renal arteries in all of the cases, and in three there was evidence of some generalized sclerosis of small arteries and arterioles.

DISCUSSION

The fact that experimental hypertension may be produced in a wide variety of animals by partial occlusion of the two main renal arteries suggests that the same mechanism might exert a like effect in man. Wilson and Byrom have reported the production of hypertension in the rat by partial occlusion of one main renal artery alone (12). The cases of hypertension reported by Boyd and Lewis (13) and by Leadbetter and Burkland (14), in which the removal of one abnormal kidney was followed by return of the blood pressure to normal levels, suggest that in the human being sufficient stenosis of one main renal artery may be a cause of hypertension. In the case of Boyd and Lewis partial occlusion of one renal artery was caused by thrombi, and in the case described by Leadbetter and Burkland one kidney lay in the pelvis and the renal artery was abnormal.

In view of this evidence it seems probable that in the cases reported here the marked stenosis of main renal arteries which was found in over half of the cases was an important factor in the pathogenesis of persistent hypertension. The role played in this respect by the more moderate narrowing of renal arteries in other cases of the series may also have been of some significance. Since the intrarenal arteries, in some of their branches, were sclerotic in every case in the series it is possible that partial occlusion of these vessels was of primary importance in the production of hypertension in many of the cases.

It may be that hypertension was initiated in these cases by a mechanism unrelated to the renal arteries. In that event the arteriosclerosis of renal arteries found at autopsy may have been an effect of the hypertension. But under these circumstances it seems likely that the hypertension would have been accentuated as the renal arteries became progressively narrowed.

Concerning the pathogenesis of acute arteriolar necrosis occurring in association with hypertension, the results obtained in experimental animals have led to the conclusion that hypertension itself is one of the factors necessary for the development of the lesions in the arterioles (5, 11, 12). This view is supported by the fact that experimental necrosis of arterioles does not develop in the kidney whose artery is partly occluded and where the blood pressure is not elevated to a

degree comparable to that in the rest of the body where the arteriolar lesions do occur.

Analysis of the relation between stenosis of the main renal arteries and the occurrence of acute arteriolar necrosis in the cases of the present series in which hypertension and vascular nephritis were both present showed necrotic arterioles in relatively few of the cases in which the main renal arteries were very narrow (reduced to a width of 1.5 millimeters or less), but in many of the cases with renal arteries of greater caliber the lesions of acute arteriolar necrosis were found in the kidneys. This evidence suggests that the pathogenesis of this form of acute arteriolar necrosis may be similar in man and experimental animals.

On the other hand the fact that the lesions of acute arteriolar necrosis *were* found in *some* of the kidneys where the main renal arteries were very narrow might suggest that both the hypertension and the arteriolar lesions were caused by a mechanism other than that which Goldblatt has shown to be effective in experimental animals.

It is evident, however, concerning the possible relation between partial obstruction of the renal arteries and hypertension, that in the human cases the caliber of the main renal arteries alone may not be a measure of the degree of partial occlusion which may exist in the vascular bed of the kidney. The degree of obstruction of the intrarenal arteries must be taken into consideration, and may be of very great significance. When marked stenosis of the main renal vessels does exist, either in association with or without narrowing of the intrarenal arteries, it seems altogether likely that such stenosis may result in the production of chronic hypertension.

It seems possible that the occurrence of acute necrosis of arterioles in the human kidney beyond a point of marked stenosis in the main renal artery might be accounted for by variations in the level of the blood pressure. In the presence of a degree of stenosis of main renal arteries sufficient to cause hypertension, an ensuing systemic pressure of 250 mm. Hg, for example, might not be associated with necrosis of renal arterioles; but if the systemic pressure should rise higher the intrarenal pressure might then rise to a level necessary for the development of the arteriolar lesions.

The five control cases in this series which showed stenosis of main

renal arteries without hypertension indicate that other factors are necessary for the development of hypertension besides partial occlusion of renal arteries alone. At the present time it is thought that experimental partial occlusion of the renal arteries is only the initial factor in a complex mechanism which is responsible for hypertension. It is supposed that renal ischaemia causes the accumulation of an increased amount of a pressor substance in the kidney (15). This material, on entering the circulating blood is believed to react on the vascular bed in such a manner as to cause hypertension by increasing the peripheral resistance to the flow of blood (16, 17).

A pressor substance, therefore, is apparently another necessary component of the mechanism responsible for the development of this type of hypertension; and it seems evident that the mechanism might fail if the pressor substance were not produced, if the reaction at the site of the peripheral vessels failed, or if the heart should fail to respond to the heightened peripheral resistance by an increase in its work.

In the two cases of polycystic kidneys in the control series, both exhibiting marked stenosis of one main renal artery without evidence of hypertension, very little renal tissue remained. It may be suggested that there was perhaps insufficient tissue to give up the pressor substance which is supposed to be one of the factors necessary for the development of hypertension.

In two other control cases with narrowed renal arteries and normal blood pressure there was rather marked atrophy of the heart. Both of the patients died from carcinoma of the bladder and were emaciated. It seems reasonable that hypertension might not develop in the presence of a diffusely atrophied myocardium, although we do not know of any experimental evidence to support this view.

In the fifth control case there was not very much narrowing of the renal vessels. One main renal artery was moderately narrowed; the other was not narrowed at all and there was little sclerosis of the intrarenal arteries.

SUMMARY AND CONCLUSIONS

On making a number of cross sections of the portions of the main renal arteries available for examination in a series of fifty cases of essential hypertension, arteriosclerotic plaques were found to project

into the lumina of the arteries in forty-three cases (86 per cent). In most of the arteries the plaques were localized in segments of the vessels near the aorta; and they caused partial occlusion which varied from a moderate degree of constriction to marked stenosis of the vessels. In two cases, besides arteriosclerotic lesions, there were old thrombi which almost completely occluded the arteries.

The lumen of one or both of the main renal arteries was stenosed to a marked degree in twenty-seven cases (54 per cent). The difference between the inside and outside diameter of the narrow arteries in this group varied from 4 to 6 millimeters. In each of five of these cases both renal arteries were nearly occluded, and in eleven other cases one main renal artery was almost completely stenosed. The lumina of the very narrow arteries of these sixteen cases were reduced to small clefts each measuring 1.5 millimeters or less in width.

In a second group of sixteen cases (32 per cent) a moderate degree of stenosis of the lumen of one or of each main renal artery was found. The difference between the inside and outside diameter of the moderately narrowed arteries varied from 3 to 3.5 millimeters.

In seven cases (14 per cent) the main renal arteries, so far as they could be examined, did not appear to be significantly narrowed. There was a difference between the inside and outside diameter of the arteries in this group which varied from 1 to 2.5 millimeters.

There was clinical and histological evidence of vascular nephritis in twenty-eight of the cases (56 per cent). Little difference was found, however, in the incidence and degree of stenosis of the main renal arteries of the cases with and of those without nephritis.

In a group of cases in which there had been hypertension and renal insufficiency, and in which therefore the lesions of acute arteriolar necrosis might occur, it was found that the arteriolar lesions were present in 28 per cent of fourteen kidneys whose main renal arteries were very much narrowed (1.5 millimeters or less in width). On the contrary, acute arteriolar lesions were found in 87 per cent of thirty-nine kidneys whose main renal arteries were narrowed but measured more than 1.5 millimeters in least diameter. The higher incidence of arteriolar lesions in the latter group of kidneys suggests that the pathogenesis of the lesions may be similar in man and experimental animals.

In all of the cases of hypertension in this series the intrarenal arteries were the site of arteriosclerotic changes; and arteriosclerotic plaques were found to cause a marked degree of stenosis of the lumen of one or both of the main renal arteries in over half of the cases. It seems not unlikely that these arterial lesions may have caused sufficient partial occlusion of the renal arteries and their branches to induce chronic hypertension by the mechanism which Goldblatt and others have shown to be effective in experimental animals.

A degree of arteriosclerosis and stenosis of main renal arteries comparable to that seen in some of the cases of hypertension was found in five of the control cases (10 per cent). In each of these control cases the state of either the myocardium, kidneys, or renal arteries themselves was such as to appear to offer a reasonable explanation for the absence of hypertension.

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EXPLANATION OF PLATES

Haematoxylin and Eosin Stains

(Photographs by Mr. Milton Kougl)

PLATE 1. MARKED NARROWING OF MAIN RENAL ARTERIES

FIGS. 1 AND 2. Right (× 9) and left (× 5) renal arteries (Case 15881).
FIGS. 3 AND 4. Right (× 6) and left (× 7) renal arteries (Case 14546).
FIGS. 5 AND 6. Left (× 5) and right (× 5) renal arteries (Case 10508).
FIGS. 7 AND 8. Left (× 5) and right (× 5) renal arteries (Case 15823).
FIGS. 9 AND 10. Left (× 5) and right (× 7) renal arteries (Case 15537).
FIG. 11. Left (× 6) renal artery (Case 15937).
FIG. 12. One of the two right (× 6) renal arteries (Case 15937).
FIGS. 13 AND 14. Left (× 4.5) and right (× 4.5) renal arteries (Case 15935).
FIG. 15. Right (× 5) renal artery (Case 15577).

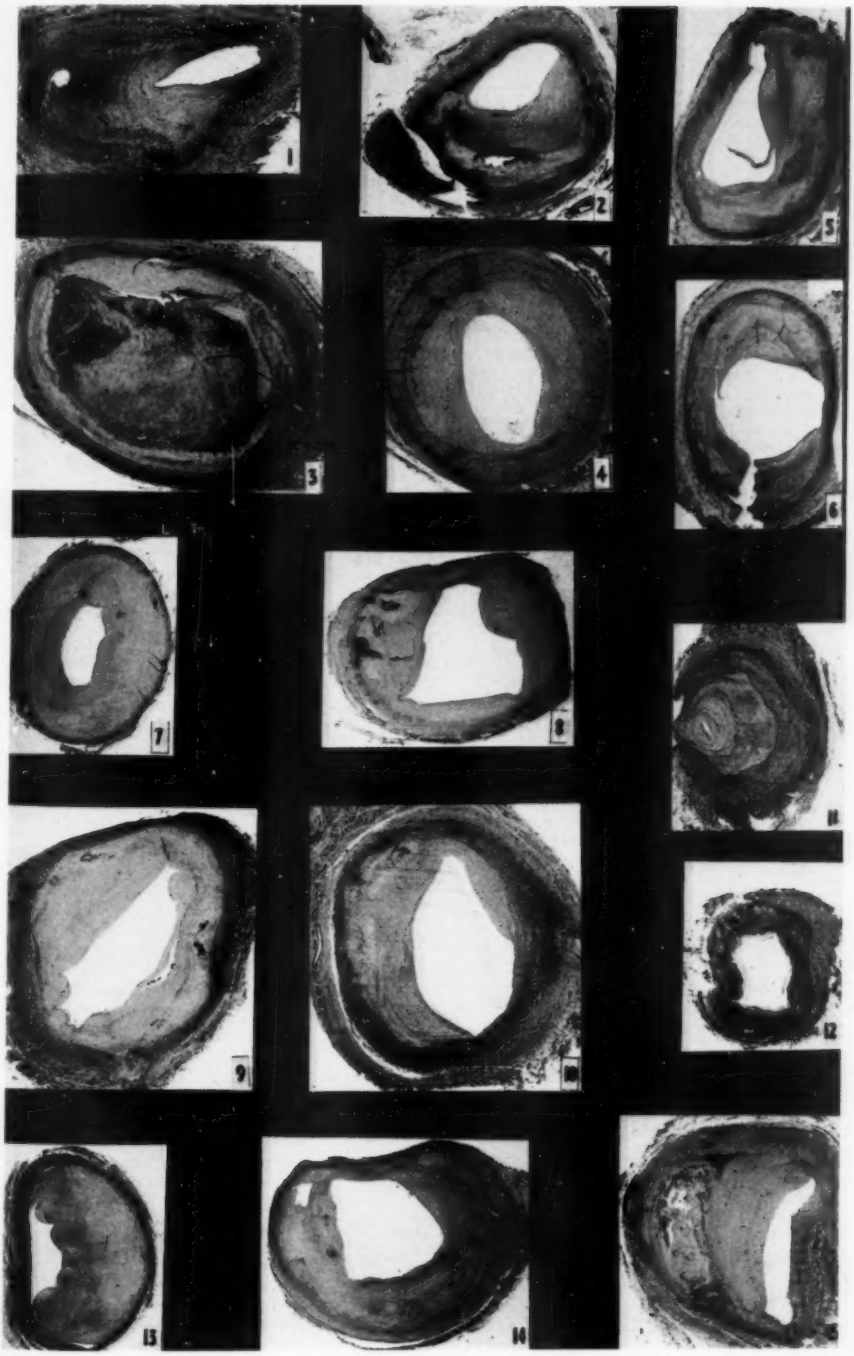
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PLATE 2. MARKED NARROWING OF MAIN RENAL ARTERIES

FIGS. 1 AND 2. Left (× 7) and right (× 7) renal arteries (Case 16237).

FIGS. 3 AND 4. Left (× 7.5) and right (× 6.5) renal arteries (Case 15509).

FIG. 5. Right (× 7) renal artery (Case 16166).

FIG. 6. Left (× 5) renal artery (Case 16097).

FIGS. 7 AND 8. Right (× 5) and left (× 5) renal arteries (Case 15652).

FIG. 9. Left (× 5) renal artery (Case 15588).

FIGS. 10, 11 AND 12. Right (× 7.5) renal artery and two branches (× 6) at hilus of kidney (Case 15928).

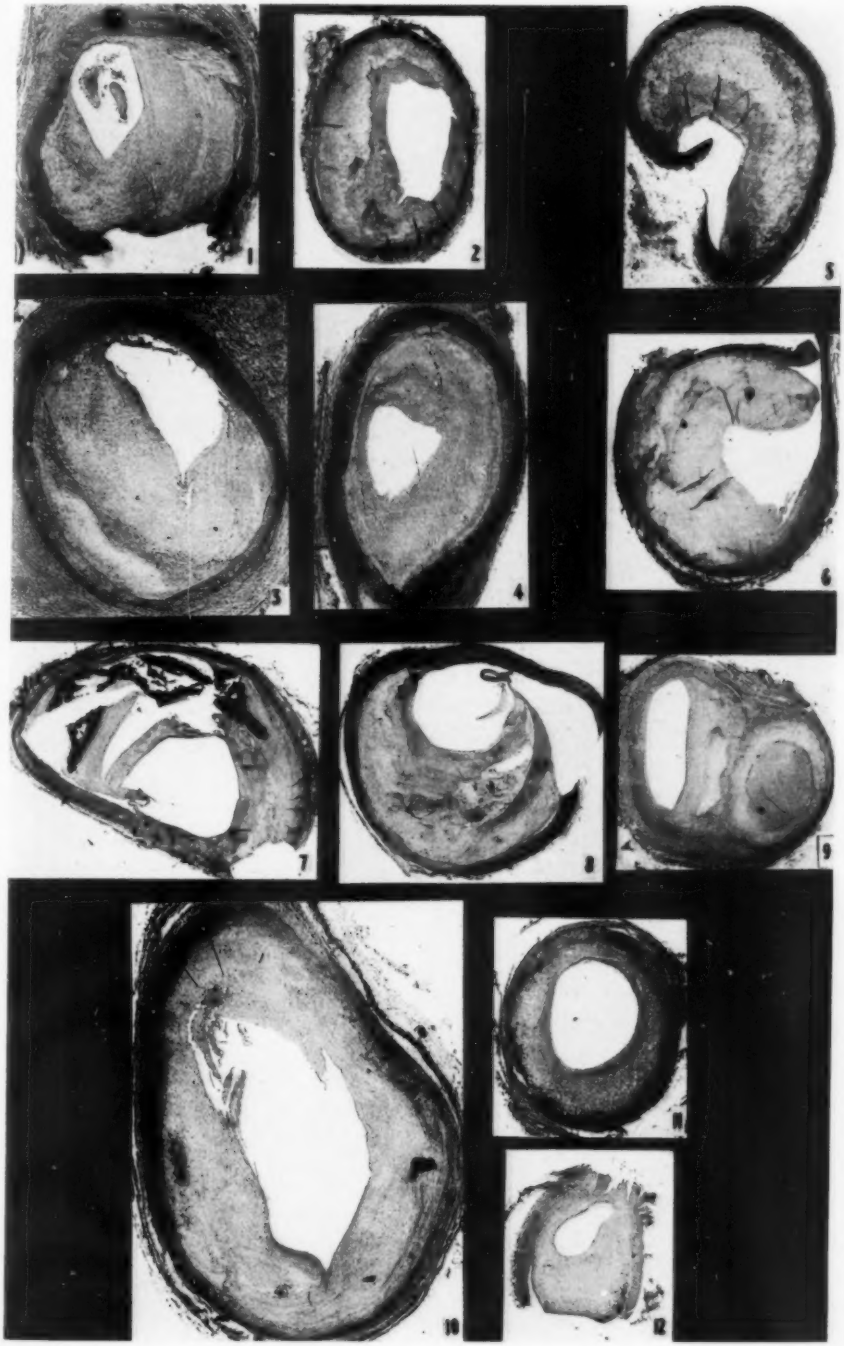
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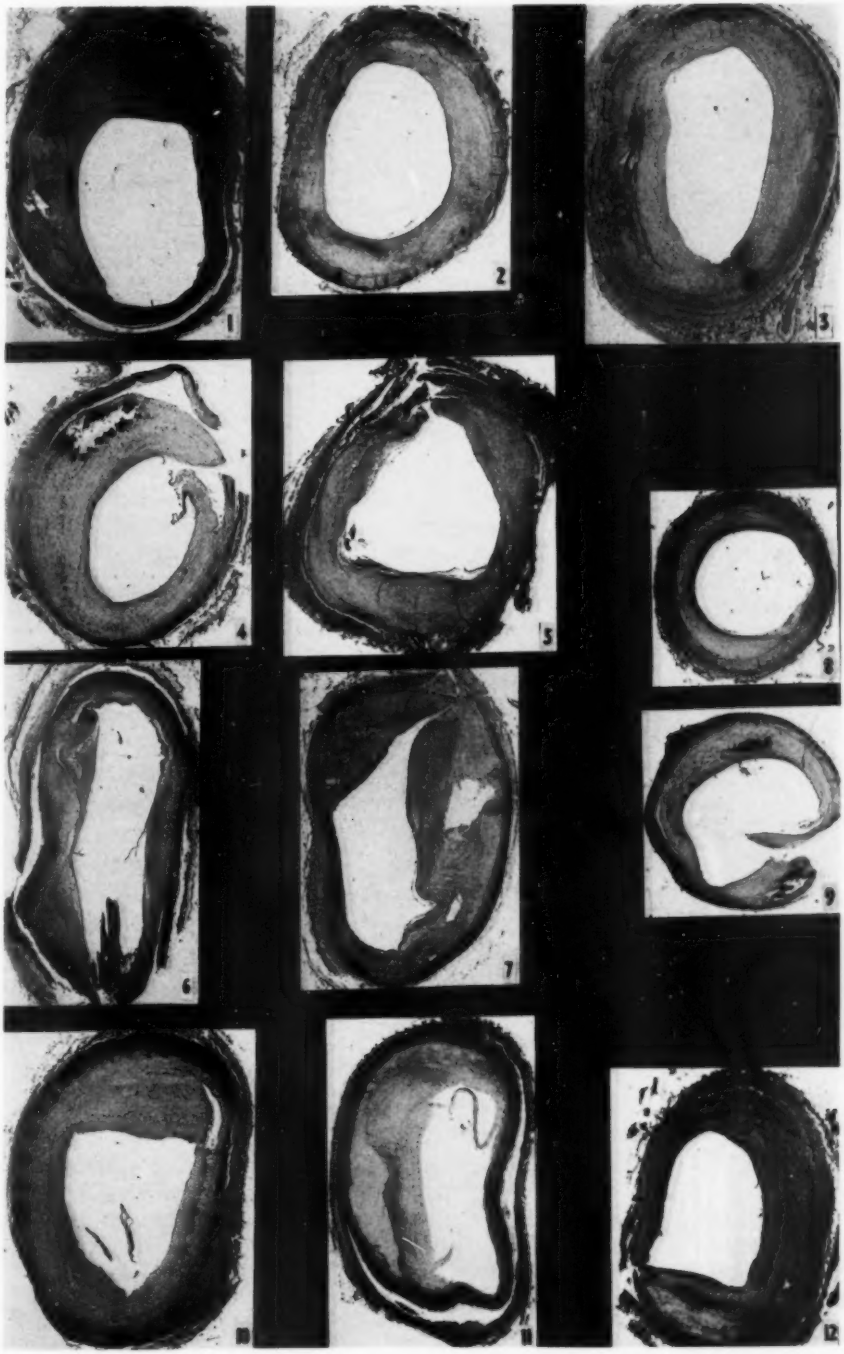
PLATE 3. MODERATE NARROWING OF MAIN RENAL ARTERIES

FIGS. 1 AND 2. Right (× 7) and left (× 6) renal arteries (Case 16150).
FIG. 3. Right (× 6) renal artery (Case 16016).
FIGS. 4 AND 5. Left (× 7) and right (× 7) renal arteries (Case 16231).
FIGS. 6 AND 7. Left (× 5) and right (× 6) renal arteries (Case 10240).
FIGS. 8 AND 9. Right (× 5) and left (× 5) renal arteries (Case 14857).
FIG. 10. Right (× 7) renal artery (Case 16207).
FIG. 11. Left (× 5.5) renal artery (Case 15704).
FIG. 12. Left (× 6) renal artery (Case 16151).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FOUR CASES OF GONOCOCCAL ENDOCARDITIS TREATED WITH SULFANILAMIDE, WITH RECOVERY OF ONE

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Although some authorities (1, 2, 3, 4) believe that the prognosis for recovery from gonococcal endocarditis is better than in the other forms of bacterial endocarditis, examples of proven cases with recovery are rare. Newman (5) reviewed the subject in 1933. If one is extremely exacting in one's criteria for establishing the presence of endocarditis and demands first, the culture and adequate indentification of the gonococcus from the blood, and secondly, the presence of a diastolic murmur at the base of the heart emanating from the aortic or pulmonic valve and appearing or disappearing under observation, then there are only three reported cases of recovery. Perry's patient (6, 7) was treated with immune and routine transfusions and with an autogenous vaccine. Newman's case (5) received one transfusion. Cromer (8) treated his patient with transfusion and Corbus-Ferry vaccine. Our criteria are somewhat stringent. Freund, Anderson and Lilly's patient (9) with gonococcal bacteremia, who developed under observation a persistent aortic systolic murmur and was treated with induced fever, probably also represents an example of recovery from a true endocarditis. There have doubtless been cases with recovery in which the mitral valve was involved; in such cases, however, it is impossible to be sure that the patient did not have merely a gonococcal bacteremia and a functional murmur in the mitral area.

Sulfanilamide and the compounds related to it having been shown to be effective in the treatment of gonorrhea, the efficacy of these drugs has also been tested in cases of gonococcal endocarditis. Orgain and Poston (10) have described a patient who came under their observation with systolic and diastolic murmurs audible over the base of the heart to the left of the sternum. Blood cultures revealed repeatedly the presence of gonococci and non-hemolytic anaerobic

streptococci. The patient was thought to have bacterial endocarditis involving the pulmonic valve; she was treated with sulfapyridine and subsequently recovered, the diastolic murmur persisting. We have not had access to the original report concerning another patient with gonococcal endocarditis reputed to have recovered following treatment with dimethyl-disulfanilamide (11).

At the Johns Hopkins Hospital 4 patients with gonococcal endocarditis have received a seemingly adequate course of therapy with sulfanilamide. Three of them died, and the diagnosis was subsequently proven at autopsy; the fourth patient recovered. Admittedly this last patient does not completely fulfill the second of the 2 criteria already suggested as necessary in establishing the presence of gonococcal endocarditis, since the diastolic murmur heard at the base of the heart was present when the patient came under observation, and has persisted. However, it seems quite likely that there was an endocarditis of the pulmonic valve; recovery was concomitant with the administration of transfusions and sulfanilamide.

CASE RECORDS

Case 1: Gonococcal bacteremia, systolic and diastolic murmurs at base of heart, nephritis, jaundice, recovery.

D. S., #123640, a 13-year-old Negress, was admitted to the Medical Service of the Johns Hopkins Hospital on April 25, 1938, complaining of chills, fever, and cough. The family history was non-contributory. The patient's general health had been excellent. She had never had severe tonsillitis, scarlet fever, chorea, or rheumatic fever. The patient stated that on exertion she had always become winded sooner than her playmates and had noted palpitation on such occasions. She had never had ankle oedema nor had she ever been noted to be cyanotic. Menstruation had begun a year before admission. She denied coitus, had noted no vaginal discharge, and had no urinary complaints. Throughout the fall and winter of 1937–1938 she had had a non-productive cough.

One month before admission the patient's family noted puffiness of her face, and she complained of frontal headache. At about the same time, the patient began to have shaking chills in the afternoon, followed by fever and sweating. These chills had become daily by the time of admission. She remained at school, however, until 10 days before admission when the cough became very severe and she became markedly dyspnoeic on exertion. A week before admission her ankles became swollen, she complained of pain to the right of the umbilicus, and she began to vomit following paroxysms of coughing. For one day she had a transient pain in the left side of the neck, but at no time did she complain of definite arthritis.

On admission, on April 25th, 1938, the patient's rectal temperature was 103.2°F., her pulse 104, her respirations 24, and her weight 118¾ pounds. The blood pressure was 120/80. She was a well-developed and well-nourished adolescent dark-skinned Negro girl. She was drowsy and peevish, but lay flat in bed in no real discomfort. She coughed frequently in paroxysms, producing only a little white mucoid sputum in which no tubercle bacilli could be demonstrated. The face and hands were puffy, and there was slight pitting edema over the sacrum and ankles. Save for an external strabismus which she had had all her life, the eyes and their fundi were normal. There was slight pallor of the buccal mucous membranes. The tonsils were enlarged. The chest was normal on percussion, but on auscultation everywhere there were sibilant and sonorous râles; these were most noticeable in the left axilla.

Heart: The neck veins were not distended. There was a systolic pulsation in the episternal notch, and a faint diastolic thrill at the base. The heart was slightly enlarged to percussion, the dullness extending 9 cm. to the left of the midline in the fifth interspace, 6 cm. to the left in the second, and 3.5 cm. to the right in the fourth. The rhythm was regular. The first sound at the apex was muffled and followed by a soft systolic murmur not heard in the axilla. In the second left interspace at the sternal border there was a loud, coarse, systolic murmur, an accentuated second sound, and a long, loud, blowing diastolic murmur. The diastolic murmur was well localized and was not transmitted down the left sternal border. In the aortic area the second sound was not as loud as it was to the left of the sternum, and the murmurs were only very faintly heard.

The peripheral vessels were not remarkable and the pulse was not collapsing. There were strong dorsalis pedis arterial pulsations. The abdomen was tense, its walls edematous, and there was shifting dullness. The liver and spleen were not palpable. There was no abdominal tenderness. Pelvic examination by a gynecological consultant revealed a marital outlet. There was no leucorrhoea and no evidence of adnexal inflammation or any other abnormality of the pelvic organs on palpation. There was no clubbing of the fingers.

Blood: R.B.C. 2.43; Hgb. 9.3 gm. (64 per cent); hematocrit 23; W.B.C. 8,700. The blood smear showed 87 per cent polymorphonuclear cells; no malarial parasites were seen and there was no sickling of the red cells.

The serological test for syphilis was negative.

Urine: Clear, yellow. Specific gravity 1.015. Acid. Sugar 0. Albumin 5 grams per liter (Esbach). On microscopic examination of the sediment there were 20 to 30 R.B.C., 5 to 10 W.B.C., and a moderate number of hyaline, granular, and red and white cell casts per high power field. Cultures of the urine were always sterile.

Venous pressure: 130 mm. of saline.

Circulation time (arm to tongue, Decholin): 10 seconds (normal).

Blood chemistry: Non-protein nitrogen 34 mgm. per 100 cc. Total plasma protein 6.4 gm. per 100 cc. A/G ratio 42/58. Van den Bergh 1.3 mgm. per 100 cc. (delayed biphasic).

The urinary phenolsulphonphthalein excretion was 55 per cent in 30 minutes, and the urea clearance 45 and 50 per cent normal standard.

Repeated electrocardiograms were normal save for a variation in the direction of T 5 and a persistent P-R interval of 0.20 to 0.22 seconds.

X-rays: A teleoroentgenogram on admission showed the width of the great vessels 4.5 cm., the maximum right diameter 3.6 cm., the maximum left diameter 8.4 cm., and the transverse thoracic diameter 23.3 cm. The heart was at the upper limits of normal in size, with an unusually straight left border due to increased prominence in the region of the pulmonic conus. There was congestion of the pulmonary vessels. An x-ray of the abdomen was normal.

Course: The diagnosis on admission was congenital heart disease with a patent ductus arteriosus, a bacterial endocarditis superimposed on the congenital lesion, and an acute diffuse glomerular nephritis secondary to the endocarditis. The fluid intake was limited to 2500 cc. daily and the patient was placed on an alkaline ash, salt poor diet. After two days of constantly sustained fever, the patient ran a hectic, intermittent fever with a "picket fence" temperature chart. Over a period of more than a week she had two shaking chills a day, at approximately 8 a.m. and 4:30 p.m. Both of these daily episodes were followed by a rapid rise in the rectal temperature to 105° with subsequently a quick fall to normal, with sweating. By May 5 the leucocytes had risen to 29,700 and the hemoglobin had fallen to 7.0 gm. (48 per cent). The urinary findings remained unchanged. The patient was drowsy at times and uncomfortable during the chills, but her general condition remained good and the edema lessened.

Venous blood cultures taken on April 25 and 27 and incubated aerobically in the routine broth, both remained sterile. However, on May 2 a gonococcal complement fixation test on the serum proved to be strongly positive; this was repeated May 9 with the same result. A venous blood culture taken on May 2, incubated in the routine beef infusion broth but under carbon dioxide tension, revealed a Gram negative diplococcus fermenting dextrose but not maltose; the same was true of an arterial blood culture on May 5. Dr. C. M. Carpenter of Rochester, New York, kindly identified the organism as a gonococcus by its fermentation and agglutination reactions. A culture from the apparently normal uterine cervix on May 5 grown under carbon dioxide on Carpenter's medium (12) produced a Gram negative diplococcus with a positive oxydase test; fermentation reactions were not carried out with this latter organism.

With this evidence of bacteremia, in view of the lack of peripheral embolic phenomena (13), the location of the murmurs, and the reputed propensity of the gonococcus for involving the pulmonic valve, the diagnosis was changed to gonococcal endocarditis with probable involvement of the pulmonic valve. Therefore, on May 6 the patient was given sulfanilamide by mouth in gradually increasing doses until by May 9 she was taking 5.4 grams daily, with 6 grams of bicarbonate of soda. She tolerated the drug very well and there was no vomiting. On May 14th the amount of sulfanilamide was increased to 7.2 grams daily, in

doses of 1.2 grams every 4 hours. This maintained the unacetylated sulfanilamide blood level at approximately 20 mgm. per 100 cc. (see Table 1).

FIG. 1. TELEOROENTGENOGRAM OF PATIENT D. S., MAY 2, 1938, ON ADMISSION

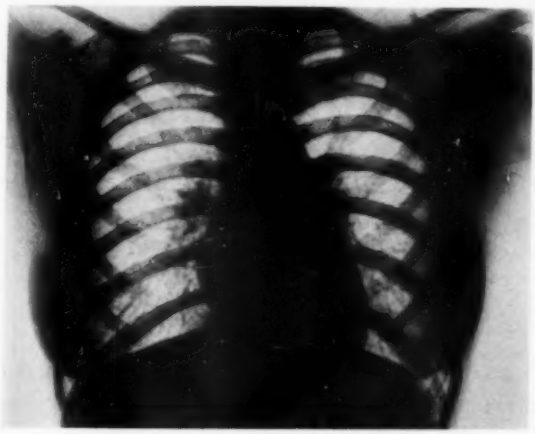

FIG. 2. TELEOROENTGENOGRAM OF PATIENT D. S., JULY 23, 1938, ON DISCHARGE

What appeared to be the effect of the drug became apparent within 48 hours of its first administration. The patient no longer had her morning chill and soon

had no chills at all, although she continued to have an evening rise in temperature to 103°. After May 13th, the eighth day of active therapy, the daily febrile peak reached only 101°. The patient became less drowsy and peevish and said she felt quite well. The white blood cell count fell to 8,000 on May 18. On May 25th, the twentieth day of therapy, the daily dosage of sulfanilamide was reduced to 5.4 gm. From May 26 to June 1 the rectal temperature remained below 100°. On the latter day the patient was started on 1.2 gm. of ferrous sulphate daily by mouth; concomitantly the temperature rose until it had reached 103.4° on June 3. There were no new physical findings, and it was concluded that the fever was due to the sulfanilamide; therefore, on June 3, the twenty-ninth day of therapy, the sulfanilamide was permanently discontinued. During the course of the next 3 days the temperature fell to normal again. Except for unexplained elevations to 100.8° on June 12, 15, and 16, the temperature remained normal until the patient was discharged. Blood cultures taken on May 19, June 3, and June 12,

TABLE 1

Level of Unacetylated Sulfanilamide in the Blood of Patient D. S.

DATE	LEVEL
	mgm. per 100 cc.
May 9	10.6
11	12.5
16	16.6
20	20.0
23	23.3
31	19.2

incubated under carbon dioxide in the routine broth and on Carpenter's medium were sterile.

During the course of this therapy the albuminuria, which had decreased to 2 grams per liter before administration of sulfanilamide, remained constant, and there was persistent microscopic hematuria. A complaint at intervals was right upper quadrant pain with muscle spasm, associated with slight scleral icterus. On one occasion the serum Van den Bergh was 2.0 mgm. per 100 cc. (delayed biphasic reaction); and there was 22 per cent retention of the dye in the half-hour bromsulphthalein test. On May 7, 13 and 15 the patient received transfusions of blood totalling 850 cc., the hemoglobin having been as low as 6.0 gm. per 100 cc. (41 per cent), on May 12. Towards the end of the period of therapy the hemoglobin began to rise spontaneously. At the same time, the size of the heart decreased, the persistent tachycardia became less marked, and the murmurs in the pulmonic area decreased in intensity so as to be inaudible at times. The diuresis, which had begun before sulfanilamide therapy, continued; the patient's weight became stationary May 27 at 89 pounds. The blood pressure was normal during her entire stay. The blood non-protein nitrogen never ex-

ceeded 42 mgm. per 100 cc. The spleen and liver were never palpable and there were never any petechiae or retinal changes. The signs of bronchitis noted on admission disappeared.

The patient was discharged on July 23, 1938, feeling well and weighing 102 pounds with no evidence of edema. A teleoroentgenogram revealed the heart to be normal in size, though there was still a slight prominence in the region of the pulmonic conus. The diameter of the great vessels was 4.2 cm., the maximum right 3.9 cm. and the maximum left 6.6 cm., with a total transverse thoracic diameter of 23.8 cm. The moderately loud, rough rather than blowing, systolic and early diastolic murmurs were best heard in the first left interspace close to the sternum; there was a faint apical systolic murmur also. There was no peripheral evidence of aortic insufficiency. The hemoglobin was 13.2 gm. (91 per cent), and the urine showed a faint trace of albumin and one or two red blood cells per high power field in the sediment. The urea clearance had risen to 72 and 81 per cent normal standard. The patient has been seen frequently since discharge,

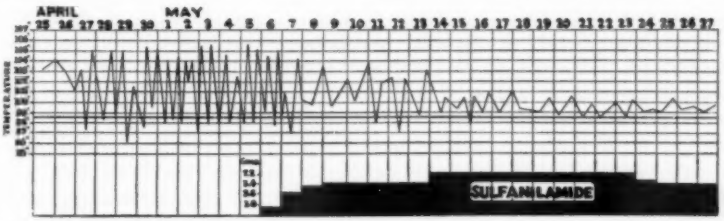

FIG. 3. CHART OF TEMPERATURE OF PATIENT D. S. DURING FIRST MONTH FOLLOWING ADMISSION; DAILY ORAL DOSAGE OF SULFANILAMIDE INDICATED IN GRAMS

having been normally active and at school with no complaints. During a four day hospital admission for check-up in November, 1938, her temperature was normal and a blood culture sterile; the renal function was normal. The electrocardiographic P-R interval remained 0.20 seconds. When last seen in May, 1939, 11 months after discontinuing sulfanilamide therapy, she was in excellent health, weighing 136 pounds. The systolic and diastolic murmurs maximum in the first left interspace persisted unchanged. The urine still showed a faint trace of albumin but no red blood cells.

Case 2: Gonococcal endocarditis of mitral valve, nephritis, hemiplegia, death.

J. R., HLH 80083, an 8-year-old Negro, was admitted to the Pediatric Service on July 13, 1938. He had been examined at this hospital in 1932 and 1933, and on both occasions his heart had been found normal. Three weeks before admission he had complained of transient, diffuse abdominal pain, and since then had had a mild sore throat and a cough and had appeared drowsy and feverish. There had been no genito-urinary or arthritic symptoms.

On admission the patient was febrile but did not appear very ill. His tonsils were large and somewhat injected. The heart was moderately enlarged and a loud, whistling systolic murmur was heard at the cardiac apex. The blood pressure was 104/50. The tip of the spleen was palpable. The genitalia were normal. Conjunctival and pharyngeal petechiae were subsequently observed.

The serological test for syphilis was negative. The hemoglobin was 8.0 grams per 100 cc. The white blood cell count was 25,000. The urine was normal. Venous blood cultures taken on July 13, 14, and 23 showed a Gram negative diplococcus. The organism fermented dextrose but not maltose and was well agglutinated by antigonococcal serum but only slightly by antimeningococcal serum. No gonococci could be cultured from the prostatic secretion.

On July 23 and daily thereafter until his death the patient received 3.6 grams of sulfanilamide by mouth. The concentration of unacetylated sulfanilamide in the blood was 10 mgm. per 100 cc. on July 25 and 9 mgm. per 100 cc. on July 29. In addition the patient received 2 transfusions, and on July 29 was given 46 cc. of antimeningococcal serum prepared in the New York State Department of Health Laboratories.

From July 13 to 23 the patient's temperature curve had been intermittent in character, with peaks at 104° daily and sometimes twice daily. As already noted, treatment with sulfanilamide was begun on July 23. From July 25 through 27 the temperature did not rise above 100°. A blood culture taken on July 29 was sterile. However, the temperature had begun to rise again on July 28 and reached 104° on July 30, the day of death. A trace of albumin and many red blood cells and casts appeared in the urine on July 28, and the same day generalized edema and retinal hemorrhages were noted. The patient's blood pressure on July 28 was 116/72. On July 29 there appeared a right hemiplegia. The temperature rose to 104° on July 30, the patient lapsed into coma, and died that day. A culture of the heart's blood taken immediately post mortem was sterile.

Autopsy (#15973) revealed a large thrombus mass on the mitral valve; gonococci could not be cultured from it nor could they be demonstrated in the smear or the routine microscopic section of the vegetation. There was an acute glomerulonephritis. An infarct was found in the right temporal lobe of the brain, but there was none in the left hemisphere.

Case 3: Gonococcal endocarditis of pulmonic valve, nephritis, hypertension, pulmonary edema, death.

F. J., #143559, a 30-year-old Negro, was admitted to the Medical Service on June 16, 1938, complaining of chills and fever. In February, 1937, he had been seen in the dispensary complaining of a soreness in his left chest which remained unexplained. A loud systolic murmur was heard at the cardiac apex. His urine was normal, as was an x-ray of his chest. Thereafter, he felt well until April, 1938, when he contracted a urethritis. Early in May he had some mild pains in the muscles with no definite arthritis. Since the middle of May he had been

subject to shaking chills, and for the week before admission he had noted generalized edema.

On admission the patient was well-nourished and in no acute discomfort. There was generalized edema, with ascites. The area of cardiac dullness was enlarged, and over the base of the heart, loudest to the left of the sternum, could be heard a coarse systolic and a higher pitched diastolic murmur. The blood pressure was 150/90. The spleen was not palpable. The genitalia were normal.

The serological test for syphilis was negative. The hemoglobin was 9.8 grams per 100 cc. and the white blood cell count 13,800. The urine had a specific gravity of 1.017, contained 5 grams of albumin per liter, and showed large numbers of red cells, leucocytes, and granular casts in the sediment. The blood non-protein nitrogen was 96 mgm. per 100 cc. and the carbon dioxide combining power 31.5 volumes per cent. Venous blood cultures, taken on June 16, 17, 18 and incubated on Carpenter's medium under increased tension of carbon dioxide showed a Gram negative diplococcus fermenting dextrose but not maltose.

The patient was thought to have a gonococcal endocarditis involving either the pulmonic or the aortic valves, with an accompanying acute diffuse glomerular nephritis. He presented a difficult therapeutic problem. He was given digitalis immediately, but his venous pressure remained elevated throughout the course of his disease and he was constantly on the verge of pulmonary edema. His renal function was markedly impaired. On July 13 the urea clearance was 30 per cent normal standard, and the renal phenolsulphonphthalein excretion was 40 to 50 per cent in 2 hours. His blood non-protein nitrogen was 132 mgm. per 100 cc. on June 24, had fallen to 52 mgm. per 100 cc. by July 27, and was 70 mgm. per 100 cc. on August 8, 2 days before death. During the patient's hospital stay his hemoglobin averaged 7.3 grams per 100 cc. despite 12 transfusions.

From June 18 through August 10 the patient was treated with sulfanilamide. The drug was given somewhat intermittently and on two different occasions was suspended for a week for fear of increasing the acidosis resultant from renal insufficiency. At no time after the onset of therapy, however, was his blood ascertained to be completely free of sulfanilamide (Table 2). The drug was administered by mouth in amounts as large as 7.0 grams a day. For the first 36 hours after admission the patient ran an intermittent fever with a chill and a subsequent rise in temperature to 102° every 12 hours. On June 19, the day after the beginning of treatment with sulfanilamide, the temperature fell and remained below 100° for 19 days, save for transient elevations following transfusions. Eventually, on July 8, the temperature rose again, and until his death the patient ran an essentially intermittent fever with daily elevations to 101° and 102°. Whether this fever may have been due to the drug itself was never satisfactorily determined. Four blood cultures taken after the onset of treatment with sulfanilamide, on June 22, July 11 and 19, and August 2, were sterile. The precordial murmurs remained unchanged. Throughout July the patient's blood pressure was elevated, averaging 175/105, and despite all therapy he died in pulmonary edema on August 10, 1938.

Autopsy (#15986) revealed almost complete destruction of the pulmonic valves, which were replaced by a mass of thrombus material. There was no evidence of any previous valvular damage of rheumatic origin. Gonococci could not be cultured from the vegetations, nor could bacteria be stained in the routine smear or section of the valve. The kidneys showed a subacute glomerular nephritis.

TABLE 2

Level of Unacetylated Sulfanilamide in the Blood of Patient F. J.

DATE	LEVEL
	mgm. per 100 cc.
June 19	5.9
20	8.9
21	7.4
22	8.5
24	6.3
25	3.6
27	2.7
29	1.0
July 5	2.8
7	4.0
9	3.5
11	5.5
13	9.4
16	10.5
20	8.6
23	1.9
27	3.1
29	4.2
Aug. 2	8.3
4	14.9
8	16.2

Case 4: Gonococcal endocarditis of mitral valve, nephritis, uremia, death.

J. C., #168316, a 27-year-old white male, was admitted to the Medical Service on April 13, 1939, complaining of fever and malaise. In June, 1938, he had an acute urethritis, which was treated with sulfanilamide by his private physician. Apparently while receiving the drug, he developed fever and jaundice. At that time examination of his heart revealed no murmurs. The sulfanilamide was discontinued, and the patient's signs and symptoms disappeared. In November, 1938 he had a febrile illness, with cough, which was diagnosed bronchopneumonia; from this illness, also, he completely recovered. Following an alcoholic spree at the end of December, 1938, there was a recurrence of the urethritis. Early in January 1939, he developed general malaise and after January 11, 1939, he ran

an irregularly elevated temperature with occasional shaking chills. These symptoms persisted and in February, 1939, he was admitted to another hospital. He was found to have developed a precordial systolic murmur and to be anemic. He received several transfusions. He was also treated irregularly with sulfapyridine. The patient's temperature ran at lower levels when he was taking the drug than when he was not receiving it. His general condition did not improve and he was transferred to the Johns Hopkins Hospital on April 13, 1939, having received no sulfapyridine since April 7.

On admission the patient was moderately emaciated and appeared chronically ill. The heart was enlarged and there was a loud blowing precordial systolic murmur, maximal at the apex. The blood pressure was 118/68. The tip of the spleen was palpable at the left costal margin. The genitalia were normal.

The serological test for syphilis was negative. The hemoglobin was 11.3 grams per 100 cc. and the white blood cell count 7,900. The urine had a specific gravity of 1.016 and showed a faint trace of albumin and 1 to 5 red cells, 5 to 10

TABLE 3

Level of Unacetylated Sulfanilamide in the Blood of Patient J. C.

DATE	LEVEL
	mgm. per 100 cc.
April 18	9.7
21	15.4
May 2	10.1
9	18.1

white cells, and granular casts on high power microscopic examination of the sediment. The blood non-protein nitrogen was 34 mgm. per 100 cc. Venous blood cultures taken on April 14 and April 17 showed a Gram negative diplococcus fermenting dextrose but not maltose; there were 10 colonies per cc. in the second culture. Gonococci could not be cultured from the prostatic secretion. A gonococcal complement fixation test on April 19 was strongly positive.

The diagnosis of gonococcal endocarditis, with involvement of the mitral valve, was made. From April 14 through 17 the patient ran an intermittent fever, with chills and subsequent elevation of the temperature to over 104°. There were 8 such paroxysms in 96 hours. From April 17 through April 21 the patient received 6 grams of sulfanilamide orally each day. The chills stopped and the daily peak of temperature dropped temporarily below 102°. Because the patient still remained febrile, sulfanilyl sulfanilamide was substituted for sulfanilamide; the patient received 1.8 grams of the former drug by mouth daily from April 23 through April 25. The patient still continued to run fever, and the sulfanilyl sulfanilamide was discontinued. Thereafter, from April 26 through May 11, when administration of the drug was finally stopped, the patient re-

ceived 4.0 grams of sulfanilamide daily. On April 28 he was given a single treatment with artificially induced fever, in the Burdick Magnatherm cabinet, the patient's temperature being maintained between 104° and 105° for 4 hours. He was transfused once during his stay in the hospital.

Despite this therapy, the patient's course was steadily downhill. Although he had only one chill after the onset of treatment with sulfanilamide, he continued intermittently and, terminally, remittently febrile. The temperature curve showed almost daily peaks at 103°. The systolic murmur persisted. Following the institution of treatment with sulfanilamide no further blood cultures were attempted using the medium (beef infusion broth to which dextrose and hydrocele fluid had been added, incubation under carbon dioxide) on which the gonococci had been originally demonstrated. Bilateral pleural friction rubs appeared and disappeared. The hemoglobin fell, levelling off at 6.2 grams per 100 cc. The white blood cell count rose to a level of 20,000. The albuminuria increased and the blood non-protein nitrogen rose steadily, reaching 134 mgm. per 100 cc. on May 16. A urea clearance test on May 11 had shown 16 per cent normal standard clearance. The patient became progressively more exhausted, lapsed into coma, and died on May 16, 1939.

Autopsy (#16406) showed a thrombus mass attached to the mitral valve with another small vegetation in the left auricle. Abundant Gram negative diplococci were seen in a smear from a vegetation, and gonococci were cultured from the heart's blood and a vegetation. There was a subacute glomerular nephritis.

COMMENT

As already noted, the patient D. S., who recovered from her illness, does not completely fulfill the most rigid criteria for establishing the presence of a bacterial endocarditis. The regularity of the temperature curve, the cardiac findings in the presence of a positive blood culture, and the nephritis make it seem likely that she suffered from a gonococcal endocarditis, probably involving the pulmonic valve. However, in view of the previous history of dyspnoea on exertion we cannot exclude the possibility that the patient may have had either a long-standing rheumatic lesion of the aortic valve or a patent ductus arteriosus, to explain the precordial murmurs, and that the present illness was merely a bacteremia without acute endocardial involvement. Recovery from simple gonococcal bacteremia is not at all uncommon (14, 15); it must not be forgotten that a transient bacteremia probably occurs in every case of gonococcal arthritis.

In evaluating the rôle of sulfanilamide in the improvement in this case (D. S.), it should be recalled that recovery from proven gonococcal

endocarditis itself has occurred following supportive therapy alone, as in Newman's case (5). Parenthetically, Horder (16) has suggested that in other forms of bacterial endocarditis the prognosis may be more favorable if, as was probable in this case, the right rather than the left side of the heart be involved.

It is of interest that this patient D. S. showed two peaks of fever daily with regularity, a finding noted by Horder (17) and recently emphasized by Williams (15) and Futcher (18) as common in gonococcal endocarditis. Further, she showed the jaundice reported as complicating the latter disease by Steiner and Walton (19), among others; in our case the sulfanilamide may also have contributed to the icterus. Finally, the patient had diffuse glomerular nephritis, which is frequently associated with gonococcal endocarditis (20).

Three patients died despite treatment with sulfanilamide. Each received the drug more or less continuously for periods of from 7 to 54 days. Blood levels of unacetylated sulfanilamide of 10 mgm. or more per 100 cc. were attained, though not always constantly maintained, in each of the three patients. One of the patients (J. R.) died following a hemiplegia presumably due to a cerebral embolus. Another (F. J.) succumbed to myocardial failure apparently due to the hypertension accompanying a severe nephritis that complicated his endocarditis. In the valvular vegetation of neither of these patients were gonococci demonstrated at autopsy. Since gonococci are notoriously difficult to cultivate, and the technique for the demonstration of bacteria in microscopic sections is not always dependable, it cannot be stated with any certainty that no gonococci remained in the vegetations. It is possible, however, that the endocardial infection had been eradicated and that, had the processes complicating the endocarditis not occurred, these 2 patients might, like D. S., have survived.

Treatment with sulfanilamide proved ineffectual in improving the condition of a fourth patient, J. C. Despite treatment with the drug over a period of 25 days and the attaining of blood levels of 9.7 to 18.1 mgm. per 100 cc., viable gonococci were present in the endocardial vegetations at autopsy. Whether the responsible organism represented a strain of gonococcus peculiarly resistant to the influence of sulfanilamide (21) was not determined experimentally.

SUMMARY

1. One patient suspected of having gonococcal endocarditis of the pulmonic valve recovered following treatment with transfusions and sulfanilamide.

2. Three additional patients, all proven by positive blood culture and subsequent autopsy to have gonococcal endocarditis, died despite treatment with sulfanilamide.

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EXPERIMENTAL STUDIES ON THE CULTURAL BEHAVIOR AND THE INFECTIVITY OF LYMPHOPATHIA VENEREA VIRUS MAINTAINED IN TISSUE CULTURE

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The causative agent of lymphopathia venerea has been recognized for a number of years to be a filter-passing virus which as yet has not been cultivated on artificial media. However, it produces in its acute stage in man a pathological picture which is totally different from that of other filterable viruses and much more like that of certain bacteria, notably *B. tularense* (7).

Because of this, the study of the virus and its relation to its host cells is one of particular interest. Since the work of Meyer and Anders (10) and of Tamura (14), it has been gradually accepted that it is possible to grow the virus in tissue cultures of different types. These authors cultivated the virus in modified Maitland media but did not make any cytological studies of the cells growing in the culture media. In 1936 Miyagawa and his associates (11) reported on the cultivation of the virus by a modified hanging-drop method using tissue fragments from the testicle, brain and spleen of normal mice. A mouse was infected by intracerebral inoculation with material obtained from the inguinal bubo of a Frei-positive patient. Later the infected mouse brain tissue was explanted into cultures of mouse testis and spleen which had been cultured for 5 days. They were able to carry the virus through two generations of tissue cultures for total periods of 10 to 13 days after the original explanation. Following such periods of incubation they found that the virus-infected cultures would kill mice in what they designated as the usual time, and they were able to stain "special granulocorpuscles" within the cells of the cultures.

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These corpuscles had previously been described in mouse brain smears by these workers.

Nauck in 1937 (12) and later his associate Malamos (9) in 1938 were able to grow the virus in tissue cultures of rabbit corneal epithelium. Virus-infected mouse brain fragments were added to 5-day-old cultures. Following the infection the membranous epithelial colonies frequently became broken up and the fragments separated into strings and islands of tissue. The cells from these fragments, when stained, appeared to be but slightly damaged, in spite of the presence of a large vacuole which developed in from 8 to 48 hours. The first sign of infection was the presence of a dark blue body near the nucleus, which took on a granular appearance, and a large vacuole in which numerous granules could be seen, the latter exactly like the well recognized "granulocorpuscles" which have been described by other authors. The cultures were followed for only 48 hours after inoculation and at that time the fluid still produced typical symptoms of encephalitis in mice.

The cytological studies here reviewed were carried out on cells infected for only a short period of time, and, so far as we know, no one has reported any cyto-pathological studies on the living infected cells. We have been able through the use of a pure strain of human fibroblasts maintained in roller-tube cultures to study the progress of a single infection in living cells for more than half a year.

METHOD

A pure strain of human fibroblasts, "R. Gi.", derived from the thyroid and which had been under continuous cultivation for 127 days (chart 1) when this investigation was begun, was inoculated with 0.3 ml. of a 20 per cent saline mouse brain emulsion. This was obtained from Dr. W. L. R. Fleming who had stored the virus at −79°C. forty days previously. This virus was obtained from an inguinal bubo of a woman who showed a positive Frei reaction.

The cultures were maintained by the roller-tube method of Gey (4) and circulation was provided by rotating the tubes at a constant speed of 12 revolutions per hour. The substrate of the culture medium used was made up of human placental cord serum 40 per cent, bovine embryo extract 10 per cent, balanced salt solution (Gey (5)) 10 per cent, and chicken plasma 40 per cent. The supernatant fluid bathing the cells had the same composition without the plasma. For microscopic observations on the living cells under oil immersion, some of the cultures studied were explanted at various stages of the infection into large lying-

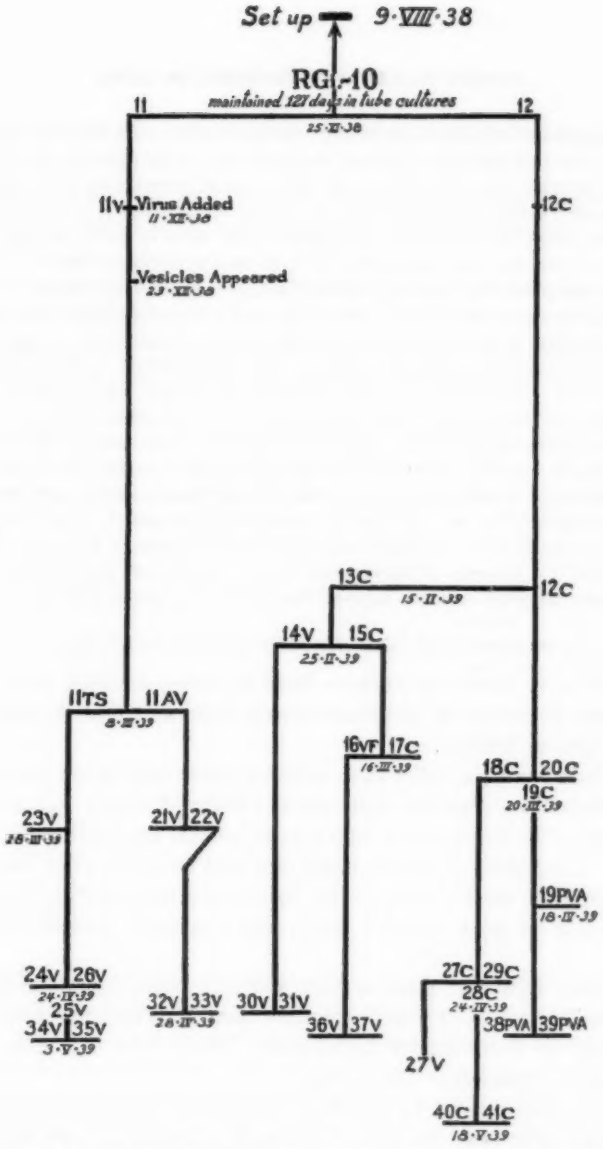

CHART 1. Life History Chart showing the time of preparation and the source of subcultures made from roller tube No. 10 of the "R.Gi." strain of human fibroblasts. The primary explantation was made from thyroid 127 days before the tubes Nos. 11 and 12 were prepared and 143 days before tube No. 11 was inoculated with virus. As noted many of the control cultures were used for test inoculations from virus (V) infected tube cultures.

drop preparations on No. 1 cover slips (40 x 45 mm.). At frequent intervals colonies were removed from the tubes on narrow No. 1 tube slips (¼ inch x 1 inch) inserted directly into the tubes, and later studied directly or after staining. Routine observations were made daily on the roller-tube cultures with the 16 mm. and 8 mm. objectives and many photographs were made of the living cells.

The supernatant fluid containing the virus was replenished every 3 or 4 days with the exception of occasional periods of 5 days. For the first half of the total time of these experiments two drops of the old supernatant fluid were carried over and added to the new medium with the idea that it might act as a constant inoculum through the period of treatment when fluid changes, substrate patches, and transfers were made. At times some of the colony transfers were made after digesting the substrate with 0.3 per cent trypsin for about 1.5 hours. Such treatment yielded naked cell colonies completely free of clot and it had little or no demonstrably injurious effect on the infected cell strain or the control cultures. Throughout the experiment about 20 colonies were maintained in each tube and these were grown in a very thin layer of the clotted medium (1–2 drops) covering the lower two-thirds of the inner wall of the tube (16 mm. x 150 mm.—*Pyrex*) and bathed by 10 drops of supernatant fluid. Subcultures and transfers were made when necessary or when colonies were needed for special purposes.

PRESENCE OF THE VIRUS IN TISSUE CULTURES

There have been four separate lines of evidence which prove that the virus is present in the tissue-culture fluid and that it multiplies in the tissue cultures.

1. Fluid from the roller-tube cultures killed mice when inoculated intracerebrally. Control fluid from uninfected tubes did not kill mice after the initial shock of an intracerebral inoculation had subsided. Fragments of mouse brain obtained from the mice killed by the infection were found to be bacteriologically sterile following inoculation of pork infusion broth and anaerobic cooked-meat infusion.

2. Fluid from the infected tube cultures when tested on known Frei-positive patients yielded positive tests, and negative tests were obtained on Frei-negative individuals. Fluid from uninfected control tube cultures gave no reaction.

3. Sera from known Frei-positive individuals were shown to have a virucidal effect upon the tissue culture fluid and prevented the death of mice, while normal sera did not have this property.

4. We have been able to follow the large vacuoles and the "granulocorpuscles" as they developed within the living cells of the tissue

cultures. We have never found either the vacuoles or the granules in uninfected tubes of the same cell strain grown under otherwise identical conditions as controls. The large and small cytoplasmic "vacuoles" which nearly always contain "granulocorpuscles" we have called *vesicles*.

In analyzing these findings in some detail let us first consider the ability of the culture fluid to kill mice. No other animal has been found to be as useful as the mouse for the continuous passage of this agent. It has been shown by various workers notably Findlay (2)

TABLE 1

DURATION OF INFECTION IN CELL STRAIN	NUMBER OF MICE INOCULATED	NUMBER OF MICE DYING	MORTALITY	PERIOD OF OBSERVATION OF MICE	CONDITION OF CULTURE AT TIME OF INOCULATION
			per cent	*days*	
34	7	7	100	7	Few cells with large clear vesicles
45	5	4	80	14	Early cell outgrowth following transfer showed no vesicles
53	20	19	95	14	Many cells with large slightly granular vesicles and some with large and small clear vesicles
89	5	5	100	16	Increased number of cells with vesicles
Total	37	35	95		
Control, normal fluid	7	0	0	21	

and Wassen (15) that the virulence and the incubation periods of the various strains of lymphopathia venerea vary tremendously. Thus it is impossible to ascribe any particular period of days from the intracerebral inoculations until the death of the animals, which might in any way be considered as pathognomonic of this virus. Our first inoculations were carried out 39 days after the original infection of the roller tube cultures and 22 days after the first visible cellular reaction to the infection. These inoculations produced death in 7 mice within a 7-day period. The total number of mice inoculated

and the results obtained may be seen in table 1. All of these inoculations were made from one line of the cell strain from tube No. 11V as shown in the life history chart (chart 1). Control fluid in all instances was relatively innocuous and did not kill any of the mice.

Secondly let us consider the ability of the tissue culture fluid to produce positive Frei tests in known Frei-positive patients. These experiments were carried out through the courtesy of Dr. M. Paulson. Tissue-culture fluid removed from the same tube which had consistently shown the ability to kill mice, produced a moderately positive reaction in three of six known Frei-positive patients and no reaction in five of five Frei-negative patients. These reactions were read nine days after the intracutaneous injection and the antigen was prepared according to Dr. Paulson's method (13).

One hundred and forty-eight days after the original inoculation of the strain, fluid from a combination of the infected tubes 30V, 31V, and 32V was tested for its antigenic power. This time the fluid produced very strongly positive reactions in five of five known Frei-positive patients. Indeed the reaction was stronger than that produced by the standard antigen. This increase in potency can probably be explained by the cytological changes which occurred in the infected tissue cultures. At this time there was a great deal more granular material present both in the cells and around them and thus there probably was a great deal more antigenic material in the culture fluid also (compare Plate I, fig. a with fig. b and with Plate V, fig. a). This is particularly interesting since the virus at this time had lost its ability to kill mice.

NEUTRALIZING POWER OF ANTISERA FROM FREI-POSITIVE PATIENTS

These experiments were originally undertaken with the idea of separating various possible strains of this virus. Strong neutralizing ability was demonstrated in eight of nine Frei-positive patients, while the ninth was only moderately positive. Serum from a normal individual had no power of neutralization in that six of six mice died within eight days. These experiments were carried out according to the technic worked out by Levaditi (6). Equal volumes of the sera and 10 per cent solutions of tissue-culture fluid made up in physiological salt solution, were mixed and incubated for one hour at room temperature. The mixture was then placed in the ice box over night

and subsequently injected into mice. This procedure does not affect the virulence of the virus in the tissue-culture fluid, as shown by the fact that a control 1:10 dilution in salt solution of the virus similarly treated except for the addition of sera, killed all of the inoculated mice within a 19 day period.

THE DEVELOPMENT OF THE INFECTION IN THE LIVING CELLS

The presence of the special "granulocorpuscles" can best be demonstrated by the photographs of stained cells which show distended vesicles full of granular material (Plate II, figs. a and b, and Plate III, fig. e). The nature of these granules will be discussed below.

The first cyto-pathological changes which we noted consisted of the formation of a few (1–10) clear vesicles in each colony twelve days after the first inoculation in tube 11V (see chart 1). Similar primary inoculations of cell-free virus-containing fluid from infected tissue cultures, made into uninfected pure cell colonies, resulted in the development of small clear vesicles. These appeared in tubes 14V and 27CV (see chart 1). Tube 14V was infected with cell-free fluid from 11V one hundred and fifteen days after the original inoculation of 11V and one hundred and three days after the appearance of vesicles therein. A tube culture from the control series 27C was similarly infected with fluid from 30V which was a subculture from 14V and vesicles appeared this time in seven days. At the time of the appearance of these vesicles in this culture tube labelled now 27CV the virus was under continuous cultivation for 6 months. As noted above it was first maintained in tube 11V for one hundred and fifteen days, transferred to a control culture 14V and maintained in it through subculture 30V for seventy-three days at which time culture 27CV was inoculated. In this culture and in other inoculated culture tubes (30V, 31V, 32V, and 33V) the specific cyto-pathological changes which have been described were observed over 7 months after the original inoculation into the strain (culture 11V).

In contrast to the findings of Malamos (9) and Miyagawa (11) who found vesicles in smears prepared 8 to 72 hours after inoculation of the tissue culture, we have never seen them in cultures of human fibroblasts in less than 7 days. Furthermore, we have observed that the vesicles persist in the cells for many weeks.

The requirements for a successful transfer of the infection in cul-

tures are apparently simple in principle but complex in execution. In order to insure that the virus comes into direct contact with the cells, we have found that it is best to digest the colonies with trypsin thus freeing them of clot. The naked cells of the colonies are then immediately exposed to the virus and tissue cultures made. Unless this is done infection does not usually take place for the virus evidently does not readily penetrate the thin barrier of the clotted medium.

When first seen the vesicles are very small (Plate I, fig. a; Plate III, fig. a; Plate IV, fig. a) and are not unlike any clear vacuole that one might observe in cultures of many different kinds of cells. These small vesicles (Plate II, fig. a) evidently represent the response of the cells to the presence of a few virus conglomerates such as the "granulocorpuscles." We have observed some large vesicles which appeared in cells which were apparently normal 24 hours previously but which had been exposed to the virus many days previously. We have not investigated the mode of entrance of the virus into living cells, but consider it a fundamental problem in virus infection.

As the vesicles grow in size one can observe an increase in the number of granules. At first there are a very few granules, irregular in size, less than 1 μ in diameter, which are observed chiefly just inside the wall of the vesicle (Plate II, figs. a and b). This distribution of the granules was observed both in the living cells and in Giemsa-stained cultures.

Later the vesicles become so large that they use up most of the cytoplasm as a shell-like cover and usually push the nucleus to one side. In this advanced stage of cell infection, these vesicles are full of closely packed uniform granules about 0.2 μ in diameter. These granules exhibit Brownian movement and diploid forms are often seen.

Such distended cells are capable of extending long processes and we have watched them migrate a great distance from the colony carrying their burden with them (Plate III, fig. b). Not infrequently the nucleus is compressed between two vesicles within the same cell, an arrangement which may occur early and persist for a long time (Plate II, fig. a and Plate IV, fig. b). Occasionally the vesicle is greatly elongated and has an irregular and notched outline (Plate

III, figs. a and c). No dividing cells with vesicles were observed. Rupture of the vesicle leaves a mass of homogeneous granular material sometimes retaining approximately the same shape as the original vesicle. Presumably the virus is thus freed to enter new host cells and start a new cycle.

Under conditions not clearly understood the vesicular reaction of the living cells may completely disappear and the virus still persist in the tissue culture. This occurred in tube 23V which first showed a decreased number of vesicles. The cells then became very granular and vesicles were entirely absent for more than 21 days when the cells again showed many small vesicles and a few large ones. Giemsa stains during the avesicular stage showed no intracellular clumps of granules which could clearly be associated with the presence of virus. The infected cells on both the tube-slip tissue culture preparations and the large lying-drop cover-slip culture preparations grew much more slowly than the normal control cell strain cover-slip and tube-slip preparations. This avesicular phenomenon, which we witnessed entirely by chance, is one of great importance for it shows that cellular infection can persist in the absence of the vesicular reaction, thus throwing doubt on any simple interpretation of the granules within the vesicles.

LOSS OF VIRULENCE

This virus when originally obtained from Dr. Fleming had shown an ability to produce about 60 per cent mortality when transferred from mouse to mouse. As may be seen in Table 1, when it was put into tissue culture, the mouse mortality was increased to almost 100 per cent. On the 53rd day a 1:50 saline dilution killed five of five mice in 13 days. But later the virus material was found to have lost its virulence in a period of 22 days during which it had not been tested. It was thus avirulent 111 days after the original inoculation of the tissue with mouse brain material.

Reference to table 2 shows that of a total of 26 mice inoculated at different times, only one died. Yet during this period the virus material was certainly present in the tissue culture as shown by its potency in producing a Frei reaction and the cytological appearance of the cells. However this definite change is open to at least two in-

terpretations: (1) the virus itself may have lost its virulence for mice, or (2) neutralizing substance may have been present within the tissue-culture tube, presumably either formed by the cells or present in some component of the medium.

Concerning the first point: A similar change in virulence has been demonstrated for the virus of fowl pox which causes very similar cytological changes in the cells of tissue cultures. Furthermore it has been shown that chickens inoculated with this avirulent fowl pox material became immune to virulent material. All of this of

TABLE 2

DURATION OF INFECTION IN CELL STRAIN	NUMBER OF MICE INOCULATED	NUMBER OF MICE DYING	MORTALITY	PERIOD OF OBSERVATION OF MICE	CONDITION OF CULTURE AT TIME OF INOCULATION
			per cent	*days*	
111 days (22V)	8	0	0	14	Many cells with vesicles and some with very long vesicles
124 days (23V)	5	1	20	56	Early cell outgrowth following transfer showed few vesicles
129 days (14V)	5	0	0	30	Many clear vesicles—large and small
138 days (30 and 31V)	5	0	0	30	Most of the cells contain large granular vesicles
143 days (33V)	3	0	0	14	Same as above
Total.....	26	1	4		

course does not exclude the presence of a neutralizing substance such as has been demonstrated by Ludford (8) for tumors grown *in vitro*.

The following small experiment indicates that the virus may still be present in a virulent form within the cells. A cell culture line (25V) which was definitely infected originally, was used for mouse injections 138 days after the original cell strain infection, at which time it was in the avesicular stage. The fluid and the colonies removed from the wall of the culture tube were injected into 3 mice intracerebrally and produced death within 25 days. Control tissue culture colonies failed to kill any of 4 mice in one month. We recognize the fact that in this experiment only a few mice were used and

that comparatively little stress should be laid on these results. Experiments are in progress to determine whether mice infected with avirulent material are immune to subsequent injections of virulent material.

EFFECT OF SULFANILAMIDE

Because of the clinical and experimental reports concerning the efficacy of sulfanilamide in the treatment of this infection we attempted to see what effect low concentrations of the drug, within the range of therapeutic blood levels, would have upon the cytopathology described above.

For this experiment two tubes were used, 21V and 22V which had shown similar cyto-pathology, *i.e.*, many large swollen granular vacuoles for a period of 13 days, and which originally had been derived from the same infected line, tube 11AV, a subculture of 11V. To one, 21V, two drops of sulfanilamide solution in balanced salt solution were added to the supernatant culture fluid, producing a concentration level of about 10 mg. per 100 cc. Within the first 24–48 hours changes were evident in the treated tube, but these were not definite until two days later when pictures were taken. As can be seen in these, the vesicles almost completely disappeared in the treated culture (Plate V, fig. b) while many were still present in the control (Plate V, fig. a). The treated tube was much more granular because of the manifest breakdown of vesicles which were filled with elementary bodies. Two inoculations of fluid from the infected tube failed to kill mice but the control fluid was also avirulent. Data on the presence of antigenic material in the sulfanilamide treated cultures are not available at this time. These tubes were followed for 14 days when an accidental bacterial infection of tube 22VS ended the experiment.

Later a somewhat similar experiment was repeated with cultures 30V and 31V with essentially the same results and with the added observation that the cells in the treated culture appeared more healthy than those in the untreated (Plate VI, figs. a, b, c). Sulfanilamide levels in this experiment were lower, *i.e.*, about 5 mg. per 100 cc. when checked by Marshall's colorimetric analysis. From these experiments we might perhaps conclude that low levels of sulfanilamide

have a definite effect on the cyto-pathological appearance of the infection, but we have no certain evidence that the virulence of the infection is altered. The cells of the treated cultures were still cytologically abnormal (Plates VI, figs. b and c).

We have studied sections of the inguinal nodes in lymphopathia, and numerous sections of rectal strictures and of colitis due to lymphopathia but so far have been unable to find any changes in these cells which could be exactly correlated with our cytological findings in living tissue cultures. In one case described elsewhere (1) plasma cells were found which contained clear bluish vacuoles and irregular calcification of a group of large vesicles of the type which we have seen and described in tissue culture. It must be kept in mind, however, that such findings are not uncommon in a large variety of other pathological material.

SUMMARY

The virus of lymphopathia venerea has been grown and maintained in continuous roller-tube cultures of a pure strain of human fibroblasts for more than seven months.

The cell-free tissue-culture fluid at first produced almost 100 per cent mortality in mice but later lost this power.

The neutralizing power of human sera from Frei-positive patients was demonstrated on virulent tissue-culture fluid.

Tissue-culture fluid from specifically infected tissue cultures serves as a good antigen for Frei tests.

Specific cyto-pathological changes were observed and studied in living cells infected with the virus of lymphopathia venerea.

Sulfanilamide in low concentration in the culture media was observed to alter the course of the specific cell reaction to the presence of the virus.

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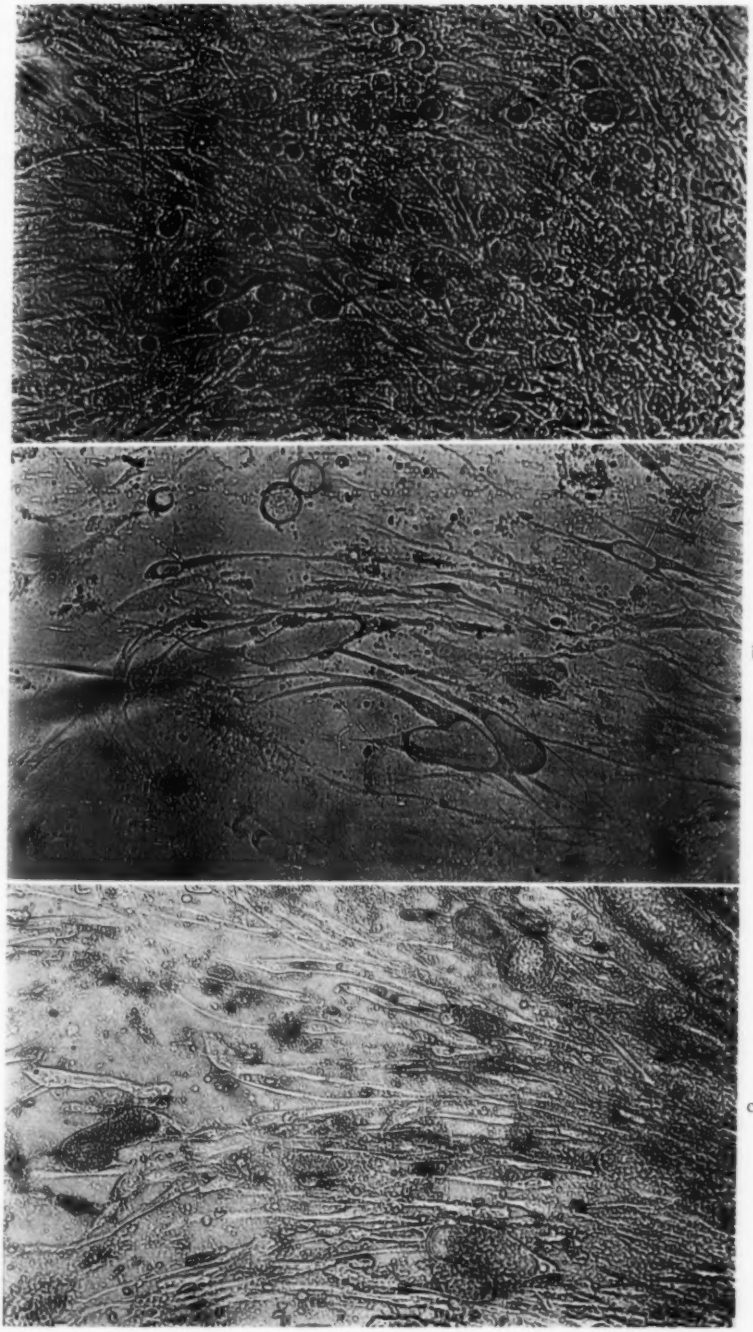
PLATE I

Cyto-Pathological Changes in Living Cells

Fig. a. Photomicrograph of early vesicles in 11V as they developed within the cells of a culture which had been infected for 70 days. (× 150)

Fig. b. Similar vesicles in the same tube at the edge of the outgrowth. One of them is notched and in general they are larger than those above and probably older. In the lower left hand corner is the granular debris resulting from the break-down of a vesicle. (× 150)

Fig. c. A later stage of the infection. This tube 30V had been infected 91 days previously. Vesicles are much more granular and there is much more granular debris between the cells. (× 150)



a

b

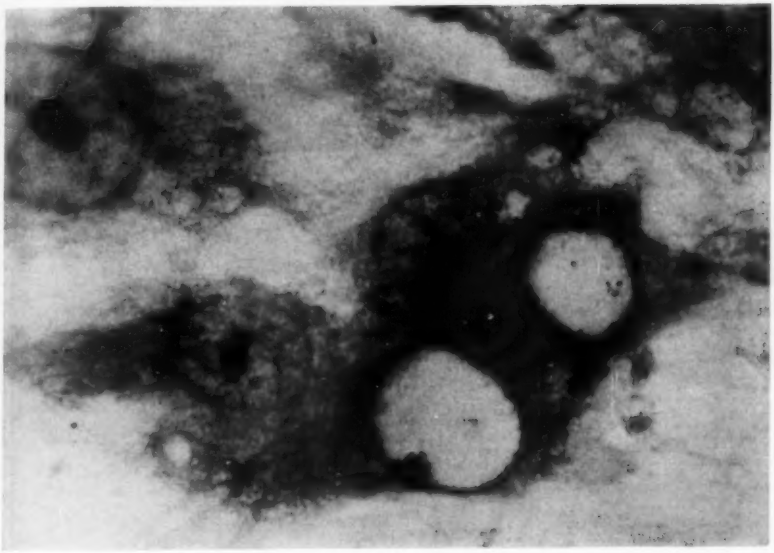
c

PLATE II

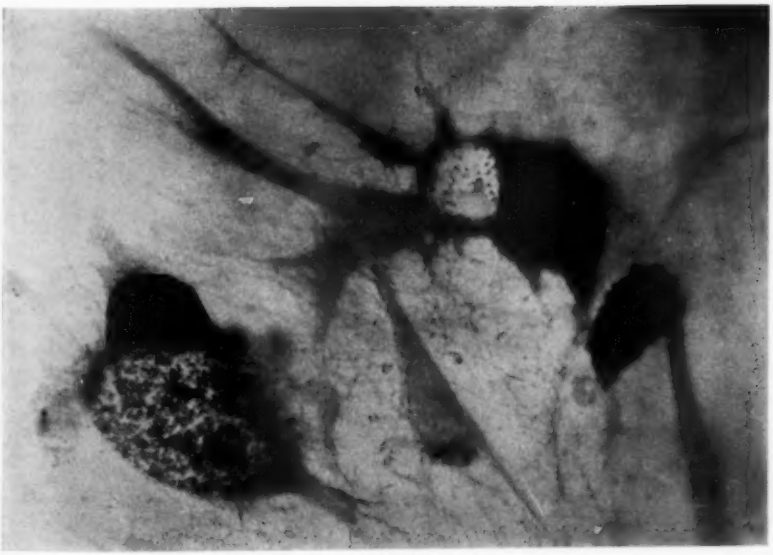
PHOTOMICROGRAPHS OF INFECTED CELLS IN FIXED AND STAINED TISSUE CULTURES

FIG. a. Very early stage of cell reaction to infection. Two small separate vesicles are shown in the central cell. In this early stage the granules are large. (Giemsa Stain. × 1500)

FIG. b. A small vesicle with few granules and a large vesicle densely packed with uniform and regular granules. The dark areas are the cell nuclei. (Giemsa Stain. × 1000)



a



b

PLATE III

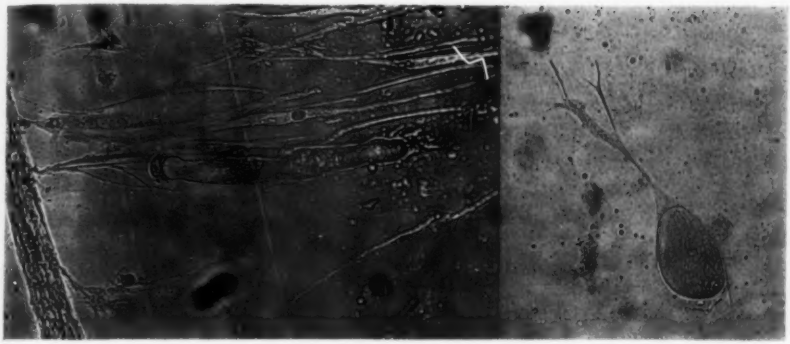
Variations in Shape and Size of Vesicles

Fig. a. A greatly elongated vesicle with an oval nucleus at one end, oriented perpendicularly to the long axis of the cell. Tube 22V. 121 days after infection. Living cells in roller-tube. (× 150)

Fig. b. An infected cell which had wandered away from the central colony. Note nucleolus within compressed nucleus at base of cell. Tube 22V. 121 days after infection. Living cells in roller-tube. (× 150)

Fig. c. High power of another elongated vesicle. This cell was studied under oil immersion during life and the granules exhibited Brownian movement. Tube 14V. 136 days after infection. Giemsa Stain. (× 1000)

Fig. d. Many cells distended with granular balloon-like vesicles. Living cells in roller-tube. (× 150)



a b

c

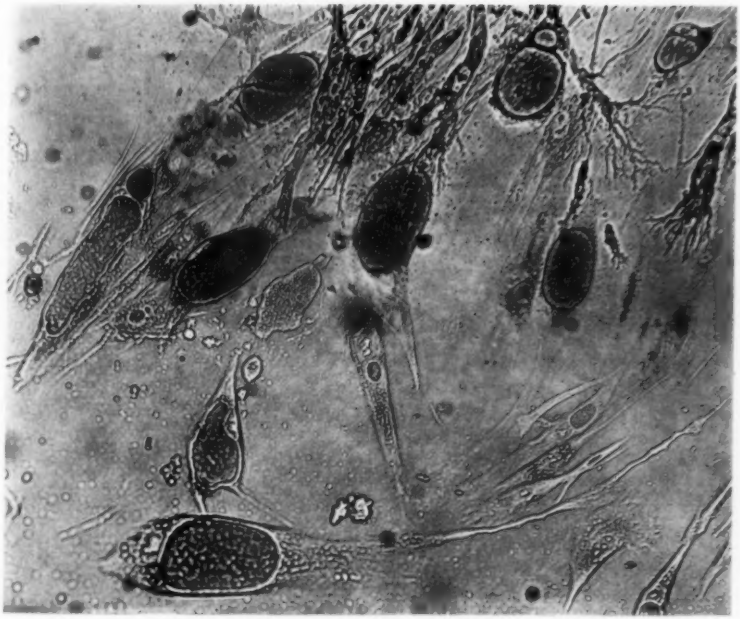
d

PLATE IV

Effect of Age on Appearance of Vesicles

Fig. a. Several cells with very small vesicles and some with large granular vesicles which appeared dark brown on direct microscopical observation of the culture. The latter vesicles remained in this shape for several weeks. Tube 33V. 146 days. Living cells in roller-tube. (× 150)

Fig. b. Another field from the same culture. Note cell in lower right hand corner with nucleus compressed between two vesicles. (× 150)



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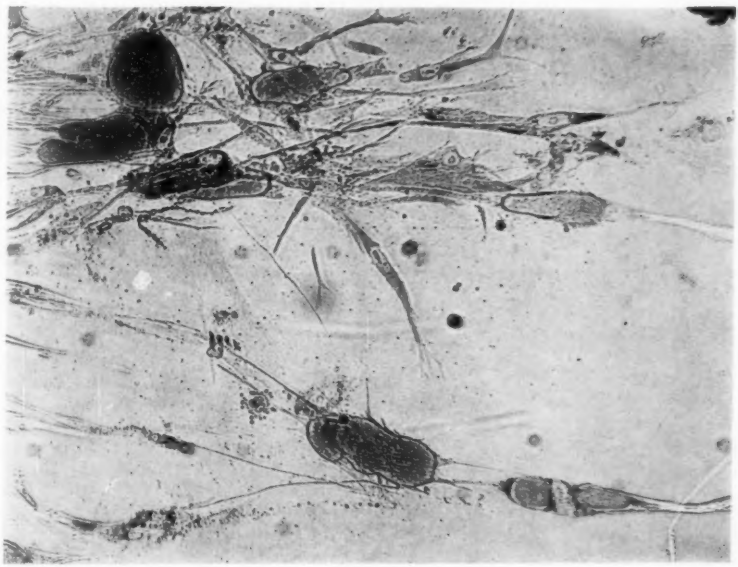


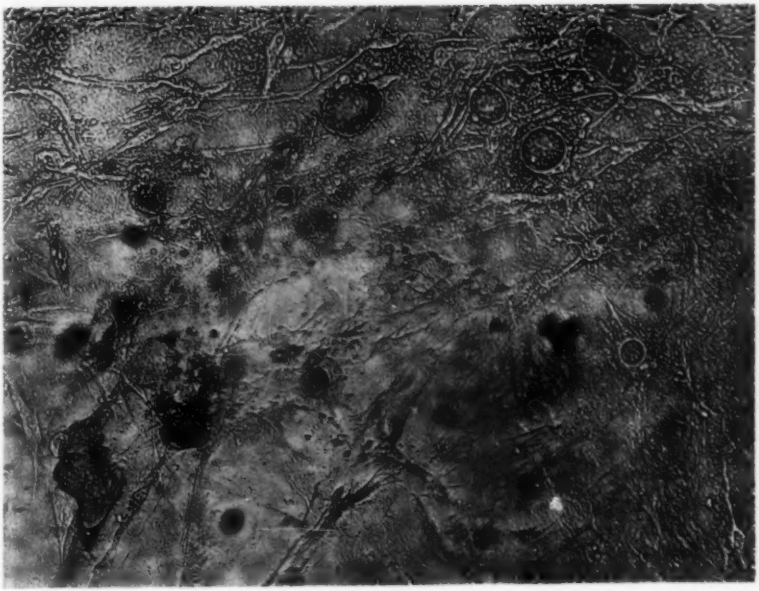
b

PLATE V

Effect of Sulfanilamide

Fig. a. Living cells in roller tube. Note numerous vesicles. Tube 22V. (Control to tube 21VS.) 118 day old infection. (× 150)

Fig. b. Roller-tube culture containing sulfanilamide, 10 mg. per 100 cc. Note absence of large vesicles and granular material. Tube 21VS. 118 day old infection. Living cells in roller-tube. (× 150)



a

b

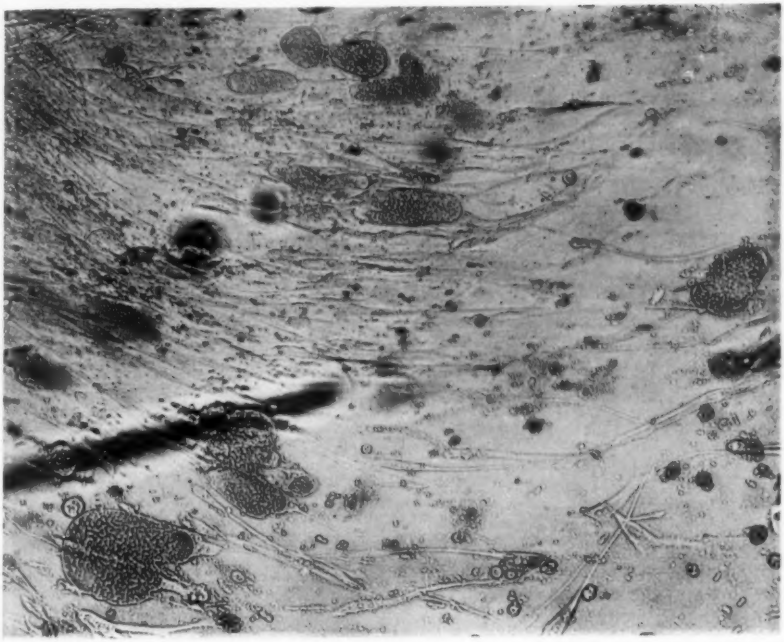
PLATE VI

Effect of Sulfanilamide

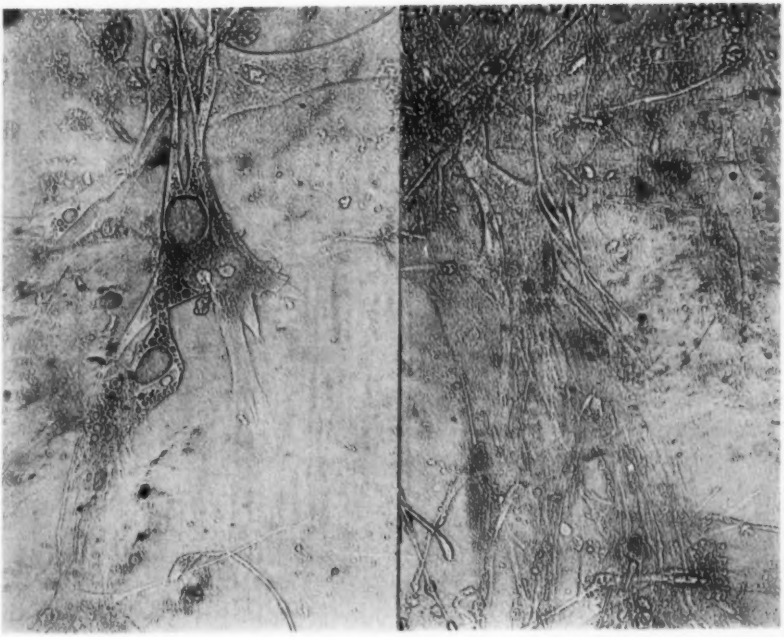
Fig. a. Living culture showing large granular vesicles and some granular debris in the medium. Tube 30V. Untreated control. (× 150)

Fig. b. A selected field showing cells with large vesicles and with many small ones throughout the cytoplasm. The latter are evidently degeneration vacuoles which appear in old cultures. Tube 31VS. (× 150)

Fig. c. An average field from the same tube. Most of the colonies had an appearance somewhat like this with good growth and no vesicles. This tube treated with sulphanilamide. (× 150)



a



b c

FACTORS INFLUENCING PLASMA PROTHROMBIN IN THE NEWBORN INFANT

II. Antepartum and Neonatal Ingestion of Vitamin K Concentrate

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In the previous article of this series (1) the relationship between the maternal and infant prothrombin levels in both term and premature deliveries was reported. Preliminary experiments were cited to show that the low infant levels could be raised by feeding vitamin K concentrate to mothers prior to delivery as well as by administering it after birth. It is the object of the present investigation to study further the possibilities offered by the antepartum and neonatal administration of vitamin K concentrate as suggested in the previous report. The plasma prothrombin level was again determined by the method of Smith, Warner, and Brinkhous (2, 3). This method was modified only to the extent that the various samples of fibrinogen were so diluted that the total nitrogen per 100 c.c. remained constant. Blood samples were taken from the antecubital veins of the mothers, from the umbilical cords at birth, and from the antecubital and external jugular veins of the infants. The results are recorded in the tables below in units of prothrombin dilution.

Tables I and II, which serve as controls in this study, are similar to the two tables in the previous paper. They have been considerably augmented, but the results are essentially similar. The slightly higher readings of both the infant and maternal prothrombin levels may be due to an increased intake of green vegetables during the summer months.

In Table III the plasma prothrombin levels of five treated mothers and five full term infants are recorded. These mothers received,

[1] Fellow, National Committee on Maternal Health.

TABLE I

The plasma prothrombin levels of mother and child, expressed in dilution units, in thirty-one full term deliveries

NAME	RACE	INFANT WEIGHT	PROTHROMBIN DILUTION UNITS	
			Mother	Infant
C. B.	W.	3,660	138.9	39.2
Z. B.	C.	2,825	202.9	13.7
R. B.	W.	4,010	201.2	33.8
E. B.*	W.	2,880	92.4	28.2
		2,800		26.8
N. B.	C.	3,305	157.0	41.3
N. B.	C.	3,600	45.0	14.0
M. C.	C.	4,075	99.0	36.5
M. C.	W.	3,120	45.8	14.8
N. E.	W.	3,290	130.6	26.8
B. F.	C.	2,465	237.6	60.4
M. G.	C.	2,535	173.2	32.2
J. G.	W.	3,620	129.8	15.0
E. H.	W.	3,550	124.4	25.6
B. H.	W.	3,800	150.5	28.6
A. I.	W.	2,360	149.9	32.6
E. J.	C.	3,040	151.8	34.4
D. J.	C.	3,000	85.0	14.9
M. J.	W.	3,850	295.4	36.0
R. K.	W.	3,310	129.8	62.5
S. M.	C.	3,180	61.6	21.3
E. R.	W.	3,920	85.8	20.0
E. S.	W.	2,670	123.8	22.4
M. S.	W.	3,110	144.0	34.4
C. S.	C.	2,760	117.0	28.4
B. T.	C.	2,675	46.2	14.2
M. T.	W.	3,700	189.0	33.7
A. W.	C.	2,675	99.8	33.8
P. W.	C.	3,775	79.2	20.5
R. W.	C.	3,010	164.3	26.6
E. W.	C.	2,470	124.4	27.7
G. Z.	W.	3,400	97.4	13.8
Average.....		3,201.2	131.4	28.6

* Double ovum twins.

under supervision, 4,500 units[2] of vitamin K concentrate[3] by mouth, daily, for varying lengths of time during the last month of pregnancy.

[2] The Ansbacher unit is used throughout (4).

[3] The vitamin K concentrate was furnished by The Squibb Institute for Medical Research.

TABLE II

The plasma prothrombin levels of mother and child, expressed in dilution units, in seventeen premature deliveries

NAME	RACE	WEEKS PREMATURE	INFANT WEIGHT	PROTHROMBIN DILUTION UNITS	
				Mother	Infant
D. A.	C.	12	1,735	130.9	0*
A. B.	C.	7	1,000	111.3	6.7
A. C.	W.	8	1,700	189.0	15.8
H. C.	W.	5?	1,545	79.9	5.0
P. C.	C.	3	2,130	123.3	13.4
M. D.	C.	13	970	141.5	6.8
J. D.	W.	9	1,210	207.3	10.9
D. D.	W.	3	2,310	127.5	21.9
E. E.	C.	6	2,275	121.8	14.0
M. L.	C.	13	970	134.8	6.6
C. M.	C.	14	830		6.8
A. M.	W.	4	1,680	191.4	13.8
E. M.	W.	3	2,160	175.9	11.2
J. M.	W.	5	1,700	143.9	13.7
N. R.	C.	8	1,500	188.2	31.9
H. T.	W.	7	1,810		0*
R. W.	C.	3	2,335	65.9	6.7
Average			1,638.8	142.2	10.9

* Amount of prothrombin too small to measure.

TABLE III

The plasma prothrombin levels of mother and child, expressed in dilution units, in five full term deliveries following prolonged treatment of the mother

NAME	INFANT WEIGHT	DAYS FROM ONSET OF TREATMENT TO DELIVERY	PROTHROMBIN DILUTION UNITS		
			Mother prior to treatment	Mother at delivery	Infant at delivery
R. S.	3,000	35	91.6	223.2	77.4
A. D.	3,080	30	85.0	168.9	92.2
B. G.	2,950	24	94.0	158.4	83.8
C. S.	2,490	17	189.8	246.3	73.8
E. R.	3,740	14	193.9	274.9	74.4
Average	3,052		130.9	214.3	80.3

Dose of vitamin K concentrate, 4,500 units a day.

Not only can the maternal plasma prothrombin be raised by this means, but the infants are born with plasma prothrombin levels three times those of the control group. Follow up studies on these

infants during the first ten days of life show that there is only a very slight decrease from the high levels at birth.

Table IV demonstrates the effect of large doses of vitamin K concentrate given by mouth to ten mothers less than twenty-four hours prior to delivery. Nine thousand units of the concentrate were administered either in one dose or two equally divided doses, two hours apart. Even with this short period of treatment both the infant and maternal prothrombin levels were raised. The average

TABLE IV

The plasma prothrombin levels of mother and child, expressed in dilution units, in ten full term deliveries following treatment of the mother during labor

NAME	INFANT WEIGHT	HOURS FROM ONSET OF TREATMENT TO DELIVERY		PROTHROMBIN DILUTION UNITS		
				Mother prior to treatment	Mother at delivery	Infant at delivery
		hrs.	*min.*			
V. P.	3,550	19	59		231.9	148.5
M. Y.	3,310	16	57		272.8	81.2
M. Z.	3,410	14	50		273.7	78.0
E. O.	3,260	12	38	221.0	261.8	72.0
E. M.	3,040	11	43	136.3	162.3	66.6
E. J.	3,080	6	57	173.7	238.3	71.5
R. B.	3,075	6	39	128.7	175.6	70.5
M. B.	3,750	4		253.4	296.0	67.7
L. S.	3,220	1	40	155.8	191.4	53.9
D. C.*	2,875	1	29		116.0	21.6
Average....	3,347.8			178.1	233.7	78.7

Dose of vitamin K concentrate, 9,000 units.

* Not included in the average. Duration of treatment too short to be effective.

of the infant levels in this series is again approximately three times that of the control group. The height to which the infant plasma prothrombin can be elevated seems, within the limits of this experiment, to vary directly with the time intervening between the administration of the concentrate and the birth of the infant.

Table V illustrates the relationship between the plasma prothrombin levels of twin infants, one of which was treated with vitamin K concentrate by mouth. Four sets of double ovum twins were studied. In each instance twin *A* received 1,000 units of the concen-

trate daily for a varying number of days, while twin *B* remained untreated. All of the infants receiving vitamin K show a steady rise in the plasma prothrombin, while the levels of the untreated twins remain fairly constant. Following the cessation of therapy the treated infant tends to maintain its high level.

TABLE V

The plasma prothrombin levels of mother and infants, expressed in dilution units, in four twin deliveries following which one twin was treated

NAME	INFANT WEIGHT AT BIRTH	AGE	PROTHROMBIN DILUTION UNITS		
			Mother	Twin A	Twin B
		days			
C. J.	A. 1,665	1	108.6	13.4	13.4
	B. 1,895	5		27.2	14.6
Therapy: Vitamin K concentrate, 1,000 units each day for four days					
M. B.	A. 2,070	1	170.2	25.6	27.5
	B. 2,330	5		36.4	27.9
		21		38.3	25.7
Therapy: Vitamin K concentrate, 1,000 units each day for four days					
F. S.	A.* 3,120	1	103.1	10.3	14.0
	B. 2,535	3		19.9	14.6
		9		24.0	15.8
		14		24.3	15.8
		21		28.6	
Therapy: Vitamin K concentrate, 1,000 units each day for eight days					
G. J.	A. 2,765	1	115.4	33.4	33.7
	B. 2,835	3		45.5	35.0
		5		56.7	34.8
		9		54.0	36.8
Therapy: Vitamin K concentrate, 1,000 units each day for four days					

* For purposes of tabulation twin *A* is always the treated infant.

The plasma prothrombin level of fourteen infants during early life is shown graphically in figure 1. These findings are in agreement with those of Brinkhous, Smith, and Warner (5) namely, that the plasma prothrombin level of the newborn infant rises extremely slowly during early life. This graph is to be compared with figure 2

which illustrates the influence of vitamin K concentrate on the plasma prothrombin of thirteen infants during the newborn period. The second group of infants received 1,000 units of vitamin K concentrate by mouth, daily, during the first four days of life. A rapid rise in the plasma prothrombin occurs during the period of treatment and the higher levels produced are fairly well maintained after cessation of

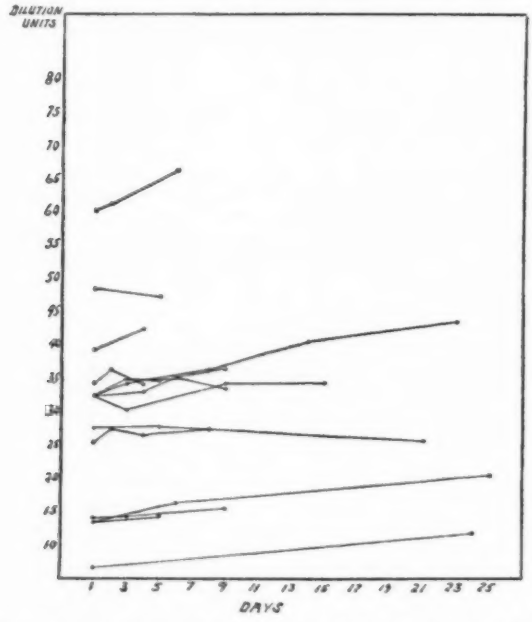

FIG. 1. PLASMA PROTHROMBIN CURVES IN FOURTEEN NORMAL UNTREATED INFANTS

the therapy. By the method used the drop in the plasma prothrombin during the first twenty-four to seventy-two hours of life, as shown by Waddell and Guerry (6), could not be demonstrated.

It is quite evident that the plasma prothrombin of the newborn infant can be significantly raised by feeding vitamin K concentrate to mothers either for a prolonged period prior to delivery or during labor. The same result, although to a lesser degree, can be obtained

by the feeding of vitamin K directly to the newborn infant. With the knowledge that 20 to 40 per cent of neonatal deaths are associated with cerebral hemorrhage and that the low plasma prothrombin level of the newborn infant may be a factor in these hemorrhages, vitamin K should serve a definite therapeutic need. While we have never seen any ill effects from the artificial raising of the plasma prothrom-

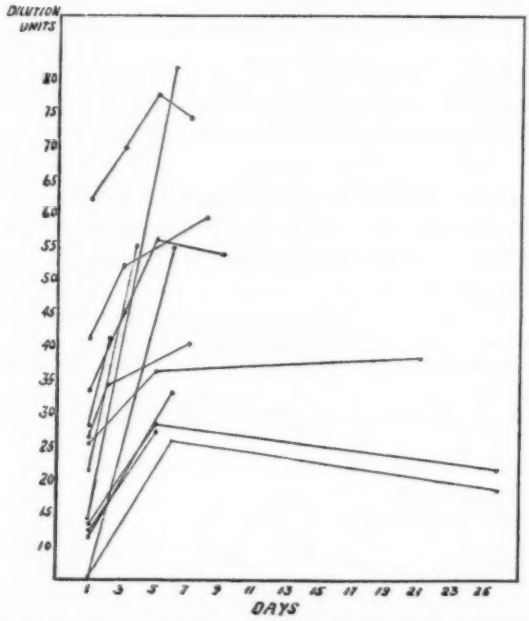

FIG. 2. PLASMA PROTHROMBIN CURVES IN THIRTEEN INFANTS TREATED WITH VITAMIN K CONCENTRATE DURING THE FIRST FOUR DAYS OF LIFE

bin, it is perhaps well to sound a note of caution at this point pending further experience. Furthermore it is by no means definitely proved that the raising of the plasma prothrombin level will, in any way, decrease the number of neonatal deaths associated with cerebral hemorrhage. The proof of this can only lie in the administration of vitamin K to large numbers of mothers. Such a study is soon to be

undertaken. For this investigation 2-methyl 1–4 naphthoquinone, the vitamin K activity of which was recently demonstrated by Ansbacher and Fernholz (7), will be used rather than the concentrate. Preliminary experiments have shown that when this substance is fed to mothers during labor, not only is a smaller dose necessary to raise the infant plasma prothrombin, but also its action occurs with much greater rapidity.

SUMMARY

1. The plasma prothrombin level of the newborn infant can be raised not only by feeding vitamin K concentrate directly to the infant after birth, but also by administering it to the mother prior to delivery.

2. The values obtained by maternal administration are often three times those normally seen, and in general are higher than those which can be attained by administering vitamin K concentrate to the baby after birth.

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BOOK REVIEWS

(The reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Diseases of the Nose, Throat and Ear. By W. WALLACE MORRISON. 675 pp. Illus. $5.50. *W. B. Saunders Company, Philadelphia, 1938.*

A text-book written primarily for the undergraduate medical student and the general practitioner. The subject matter has an orderly presentation with clarity and brevity. The author has striven to be practical rather than theoretical. The modern viewpoint is given and many antiquated ideas are discarded. The illustrations, drawn by the author, are numerous, simple, and for the most part, diagrammatic. The bibliography is scant but well selected.

N. F. A.

Textbook of Clinical Neurology. By ISRAEL S. WECHSLER. 4th ed. Revised. 844 pp. Illus. $7.00. *W. B. Saunders Company, Philadelphia, 1939.*

This well known textbook has just been revised for the third time. The discussion of neuritis has been partially rewritten and new material added including the olfactory tests of Elsberg, a brief description of the carotid sinus syndrome, petrositis, the premotor syndrome and electroencephalography. There is a section devoted to the neuroses and another to the history of neurology.

F. R. F.

A Textbook of Surgery. By American Authors. Edited by FREDERICK CHRISTOPHER. Second edition, revised. 1695 pp. Illus. $10.00. *W. B. Saunders Company, Philadelphia and London, 1939.*

The second edition of Christopher's Textbook of Surgery has surprisingly few alterations from the first edition. This fact is in reality a commentary on the excellence of the original work. The new material that has been added and the changes that have been made are a record of the advances in surgical knowledge during the past three years. A particularly good chapter on wounds by Mont R. Reid has replaced the former one. The plan to have a single volume textbook written by authorities on the various surgical subjects is certainly a wise one, and Doctor Chirstopher has been fortunate in the selection of his co-authors.

W. M. F.

Fever and Psychoses. A Study of the Literature and Current Opinion on the Effects of Fever on Certain Psychoses and Epilepsy. By GLADYS C. TERRY. 167 pp. $3.00. *Paul B. Hoeber, Inc., New York, 1939.*

This little book, dedicated to Dr. Frederick Tilney, is one of the last tangible evidences of Dr. Tilney's later concern that the Neurological Institute's research

program should actually cover the field of responsibility of the Institute: a responsibility which went deeply into the psychiatric field.

The survey is thoroughly done, in the manner one has come to expect to Mrs. Terry, and the interested reader will find in it a digest of much that he would want to know.

Dr. Tilney did not live to see the completion of the work, but he surely would have been pleased with it, as well as with the affection of its sponsors.

W. M.

The Physiology and Pharmacology of the Pituitary Body. By H. B. VAN DYKE. Volume 2. 402 pp. Illus. $4.50. *University of Chicago Press, Chicago, 1939.*

The first volume published in 1936 reviewed about 3,500 papers and in this volume references are recorded in the same way to about 1,500. The enormous outpouring of publications on this subject makes it evident that such a book must be chiefly valuable as an index of what has been written since there is so much disagreement in the results of various writers on such a great variety of experimental studies that it must be difficult for any editor to reach and express a final conclusion as to the real truth which will prevail even until the next volume appears. The author realises this and at the end of each of several chapters expresses the idea that until the hormones can be isolated in absolute purity, their effects cannot be surely known—even, for example, in the case of the growth hormone there is said to be a question of an impurity as the important factor. Further, that the presence of the intact hypophysis makes it important to use hypophysectomised animals to test the actual effect of a single hormone.

But, although there is so much that cannot easily be transferred to human conditions, from the experimental studies in remote forms of lower animals, the book is very useful in presenting a rapid survey of what has been done up to 1938.

W. G. M.

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